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Indian Journal of Chemistry
Vol. 26B, December 1987, pp. 1111-1112

Communications

A Facile Synthesis of Functionalised Organic Sulphides

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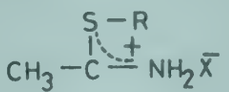
Received 29 *September* 1987; *accepted* 16 *November* 1987

Thioiminium salts and organic halides or Michael acceptors, in the absence of solvent and at ambient temperature, give title compounds in excellent yields.

Reactions of thiols with organic halides and Michael acceptors for procuring functionalised organic sulphides as useful intermediates in organic synthesis[1], are handicapped by the difficulties in obtaining functionalised thiols. When such thiols are generated *in situ* from the corresponding organic halides through their thioiminium salts and a base as such or under PTC conditions, their further reactions are plagued by the formation of disulphides[2,3]. PTC reactions have been performed beneficially in the absence of solvent[4]. This led us to perform the potassium hydroxide induced reactions of thioiminium salts with organic halides and Michael acceptors in the absence of any solvent at ambient temperature. As per expectation, these reactions proceeded instantaneously forming products in excellent yields, practically without any disulphide contaminant. Use of PT catalyst (TEBACl) did not affect the reactions.

For introducing different functionalities in the sulphides (Table 1), variously functionalised thioiminium salts (**1-3**) derived from thioacetamide and benzyl, allyl or ethoxycarbonylmethyl halides were condensed with organic halides or Michael acceptors possessing keto, ester and cyano moieties.

In a typical experiment, fused potassium hydroxide (3 mmol) was added to a mixture of thioiminium salt (3 mmol) and organic halide or Michael acceptor (3 mmol) at ambient temperature. The reaction was ex-



1. R = $-CH_2C_6H_5$, X = Cl
2. R = $-CH_2-CH=CH_2$, X = Br
3. R = $-CH_2COOEt$, X = Cl

Table 1—Functionalised Organic Sulphides Synthesised[a]

Sl No.[b]	Organic halide/Michael acceptor	Sulphide	Yield (%)	Ref.
		With thioiminium salt (**1**)		
1	$C_6H_5COCH_2Br$	$C_6H_5CH_2SCH_2COC_6H_5$	92	2
2	$CH_2=CHCH_2Br$	$C_6H_5CH_2SCH_2CH=CH_2$	75	2
3	$EtOOCCH_2Cl$	$C_6H_5CH_2SCH_2COOEt$	65	2
4	$CH_2=CHCOOEt$	$C_6H_5CH_2S(CH_2)_2COOEt$	90	5
5	$CH_2=CHCN$	$C_6H_5CH_2S(CH_2)_2CN$	85	6
6	$C_6H_5CH=CHCOC_6H_5$	$C_6H_5CH_2SCH(C_6H_5)CH_2COC_6H_5$	80	7
		With thioiminium salt (**2**)		
7	$C_6H_5CH_2Cl$	$C_6H_5CH_2SCH_2CH=CH_2$	80	2
8	$EtOOCCH_2Cl$	$CH_2=CHCH_2SCH_2COOEt$	75	2
9	$CH_2=CHCOOEt$	$CH_2=CHCH_2S(CH_2)_2COOEt$	76	8
10	$CH_2=CHCN$	$CH_2=CHCH_2S(CH_2)_2CN$	70	9
		With thioiminium salt (**3**)		
11	$C_6H_5CH_2Cl$	$C_6H_5CH_2SCH_2COOEt$	70	2
12	$CH_2=CHCH_2Br$	$CH_2=CHCH_2SCH_2COOEt$	70	2
13	$CH_2=CHCOOEt$	$EtOOCCH_2S(CH_2)_2COOEt$	70	10
14	$CH_2=CHCN$	$EtOOCCH_2S(CH_2)_2CN$	70	6

(a) All the products except at Sl Nos 1 and 6 are liquids and were purified by column chromatography and their data are identical with those reported in literature.

(b) Sl No 1 was prepared using solid reactants and crystallised from ethanol, m.p. 85° (lit.[2] m.p. 85°). Compound at Sl No. 6 was also prepared using solid reactants and crystallised from ethyl acetate, m.p. 71° (lit.[7] m.p. 72-73°). In the case of Sl Nos 3, 10, 13 and 14 minor amount of disulphides were also formed.

othermic (When one of the reactants was a liquid and the other a solid, the latter dissolved with rise in temperature of the reaction mixture. Even solid reactants on mixing at room temperature formed a molten mass). The reaction mixture was stirred or shaken and after completion (TLC, 2 to 10 min) of the reaction, it was treated with water. After extractive work-up, the product was purified by recrystallization or by column chromatography over a column of silica gel using petroleum ether (40-60°) as an eluent.

References

1 Peach M E, *The chemistry of the thiol group*, Part 2, edited by S Patai (John Wiley, New York), 1974, pp. 721-784.

2 Singh H, Batra M S & Singh P, *Indian J Chem*, **24B** (1985) 131.

3 Singh P, Batra M S & Singh H, *J chem Res (S)*, (1985) 204.

4 Bram G, Loupy A & Sansoulet J, *Israel J Chem*, **26** (1985) 291.

5 Wolfe S, Kazmaier P M & Auksi H, *Can J Chem*, **57** (1979) 2412.

6 Hurd C D & Gershbein L L, *J Am chem Soc*, **69** (1947) 2328.

7 Dodson R M & Seyler J K, *J org Chem*, **16** (1951) 461.

8 Bowie J H, Cobb D B, Dalgaard L, Madsen J O & Lawesson S O, *Aust J Chem*, **22** (1969) 1207.

9 Tokmurzin K Kh, Kozhabekov Zh E & Kuanyshkaliev K A, *Zh org Khim*, **17** (1981) 443.

10 Shostakovskii M F, Rabinovich M S, Levitov M M, Verkhovtseva T P, Preobrazhenskaya E V, Kulikova G N & Kalinovskii O A, *Zhur Obsch Khim*, **31** (1961) 1453.

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Vol. 26B, December 1987, pp. 1113-1114

Synthesis of 5-Oxalaurene, 5-Oxaepilaurene & 5-Oxaisolaurene via Radical Cyclisation Reaction

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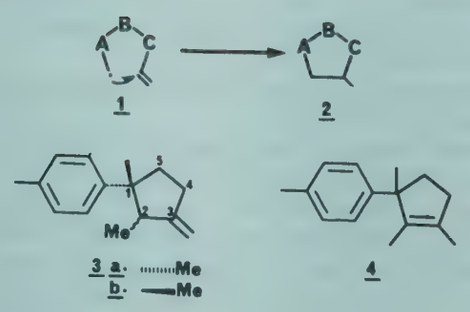
Received 19 *October* 1987; *accepted* 6 *November* 1987

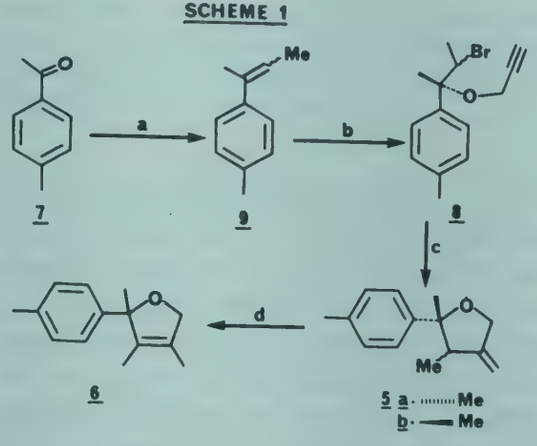
A short synthesis to 5-oxa analogs of the sesquiterpenoids, laurene (**3a**), epilaurene (**3b**) and isolaurene (**4**) using the radical cyclisation reaction as the key step is described.

The use of free radical intermediates in organic synthesis has until recently been limited to studies having more mechanistic bias. However, intramolecular radical addition reactions, i.e. radical cyclisation reactions, are now widely accepted as a powerful tool in organic synthesis by virtue of their mild reaction conditions and the stereo- and regiospecific nature, e.g. **1**→**2**, in the construction of five-membered rings[1]. In continuation of our interest in this area[2], we now describe the application of this powerful tool in the short, regiospecific synthesis to 5-oxa analogs of the sesquiterpenoids, laurene (**3a**), epilaurene (**3b**) and isolaurene (**4**).

Laurene (**3a**) and isolaurene (**4**) were first isolated by Irie *et al.* from *Laurentia glandulifera*[3,4] and more recently from the marine red algae *Laurentia elata*[5] along with several oxygenated and brominated sesquiterpenoids. Our approach toward 5-oxalaurene (**5a**), 5-oxaepilaurene (**5b**) and 5-oxaisolaurene (**6**) starts from the readily available *p*-methylacetophenone (**7**) and involves the radical precursor bromopropargyl ether (**8**) as depicted in Scheme 1. Thus, Wittig olefination of **7** with triphenylphosphonium ethyl bromide (THF, *n*-BuLi) furnished a 1:1 E, Z mixture of trimethylstyrene (**9**) in ~75% yield, which was used in the next step without separation of isomers[6]. The olefin mixture **9** was transformed to the requisite radical precursor, bromopropargyl ether **8** *via* the bromoetherification reaction using N-bromosuccinimide (NBS) and propargyl alcohol to afford a mixture of diastereomers, separable by silica gel chromatography, in over 80% yield[6]. The key radical cyclisation **8**→**5**, was best achieved (85% yield) using *in situ* generated catalytic tri-*n*-butyltin hydride ($^nBu_3SnCl - NaCNBH_3$)[2] in the presence of a catalytic amount of azobisisobutyronitrile. As



SCHEME 1



a. $Ph_3P^+C_2H_5\ Br^-$, THF, n-BuLi, 0-25°C, 2 hr; b. NBS, HC≡C-CH_2OH, -10°C to RT, 2 hr; c. $^nBu_3SnCl$ (0.15 eq.), $NaCNBH_3$ (1.5 eq.), ^{t}BuOH, AIBN (cat), 80°C, 1.5 hr; d. p-TSA, C_6H_6, 70°C, 2 hr.

expected, either isomer of **8** or the mixture on radical cyclisation generated the same mixture (1:2) of 5-oxalaurene (**5a**) and 5-oxaepilaurene (**5b**), as it is already established[1] that the rate of equilibration of the intermediate radical is faster than that of cyclisation. The structures of **5a** and **5b** were derived from their spectral data[6], in particular the high field methyl doublet at δ 0.7 for **5a** (because of its *cis*-relationship with the aromatic ring) and at δ 1.05 for **5b**, similar to those observed for the laurene and epilaurene[3b]. Finally the mixture of **5a** and **5b** was transformed to 5-oxaisolaurene (**6**) by treatment with a catalytic amount of *p*-toluenesulfonic acid in benzene.

In conclusion, we have briefly illustrated the utility of the radical cyclisation reaction in the construction of tetrahydrofuran with an exo methylene moiety.

References and Notes

1 (a) Selectivity and synthetic application of radical cyclisation reactions, Tetrahedron symposia (in print) edited by B Giese Tetrahedron, **41** (1985) 3887-4302; (b) Srikrishna A, *Curr Sci*, **56** (1987) 392.

2 (a) Srikrishna A, *Chem Commun*, (1987) 587; (b) Srikrishna

A & Pullaiah K C, *Tetrahedron Lett*, (In press); (c) Srikrishna A & Sunderbabu G, *Tetrahedron Lett*, (In press).

3 (a) Irie T, Yasunari Y & Suzuki T, *Tetrahedron Lett*, (1965) 3619; (b) Irie T, Suzuki T, Ito S & Kurosawa E, *Tetrahedron Lett*, (1967) 3187.

4 For a recent synthesis see Taber D F & Anthony J M, *Tetrahedron Lett*, (1980) 2779.

5 Hall J G & Reiss J A, *Aust J Chem*, **39** (1986) 1401.

6 Spectral data of **9** (mixture of *E, Z* isomers); IR: 1510, 835, 810 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 6.95 (*s*) & 7.0 (*ABq*), 5.7 & 5.45 (1H, 2×*q*, *J*=7 Hz), 2.3 (3H, *s*), 1.95 (3H, *bs*), 1.75 & 1.55 (3H, 2×*d*, *J*=7 Hz). For **8** (mixture of two diastereomers): IR, 3290, 2125, 1510, 1095 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 6.9-7.4 (4H, *m*, aromatic), 4.15 & 4.05 (1H, 2×*q*, *J*=7 Hz, $-CHBr-$), 3.8 (2H, *d*, *J*=3 Hz, $-OCH_2-$), 2.3 (3H, *s*, Ar−Me), 2.2 (1H, *t*, *J*=3 Hz, ≡CH), 1.7 (3H, *s*, Me), 1.65 & 1.35 (3H, 2×*d*, J=7 Hz, Me). For **5a** & **5b** (1:2): IR, 1665, 1515, 1450, 1080, 1040, 1020, 885, 820 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 6.8-7.4 (4H, *m*, aromatic), 4.8 (2H, *m*, olefinic), 4.35 (2H, *m*, $-OCH_2-$), 2.6 (1H, *m*, allylic), 2.3 (3H, *s*, Ar−Me), 1.6 & 1.25 (3H, 2×*s*, Me), 1.05 & 0.7 (3H, 2×*d*, *J*=7 Hz, Me). For **6**: IR, 1510, 1070, 1045, 1020, 815 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.0 (4H, *AB q*), 4.45 (2H, *m*), 2.25 (3H, *s*), 1.6 (3H, *bs*), 1.5 (3H, *s*), 1.45 (3H, *bs*).

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Synthesis of N-Acetyl Derivatives of (1*R*, 5*R*)-6-Aza-2-oxabicyclo[3.3.0]-octan-3-one & (1*S*,5*R*,8*R*)-8-O-Benzyl-6-aza-2-oxabicyclo[3.3.0]octan-3-one from D-Glucose†

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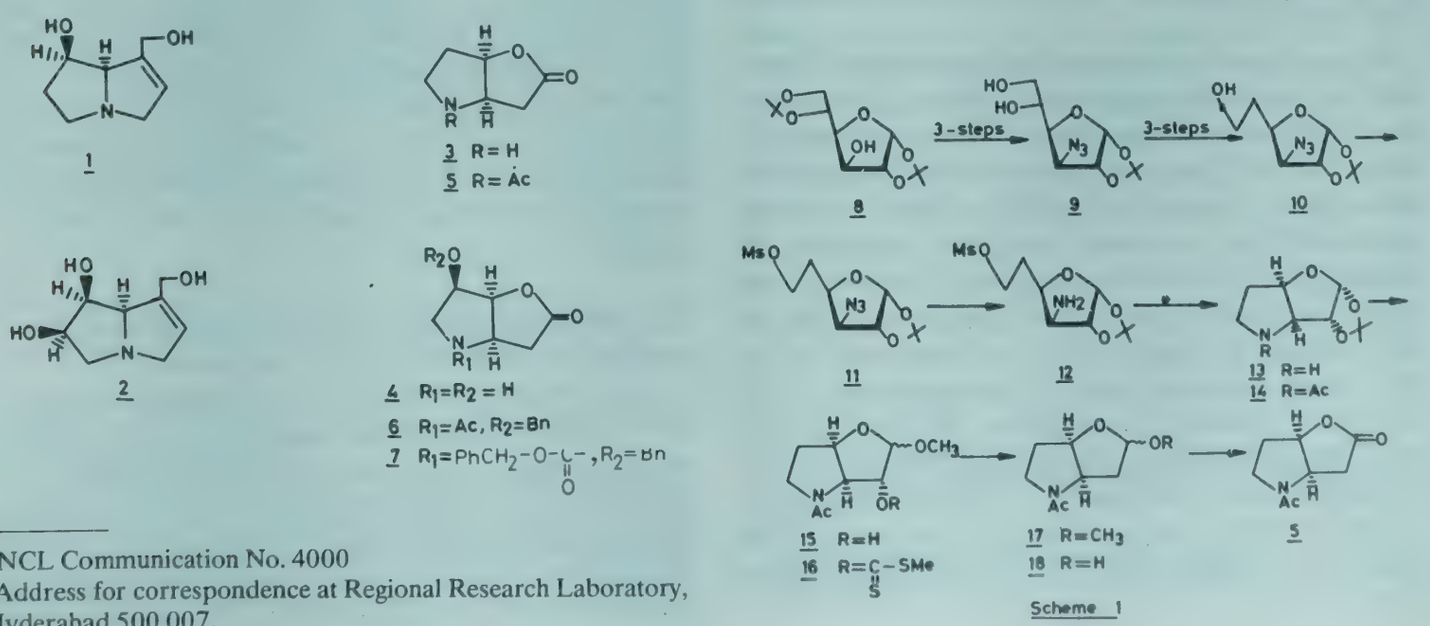
N-Acetyl derivatives of (1*R*,5*R*)-6-aza-2-oxa-bicyclo[3.3.0]octan-3-one (**5**) and (1*S*,5*R*,8*R*)-8-O-benzyl-6-aza-2-oxa-bicyclo[3.3.0]octan-3-one (**6**), suitable chiral intermediates for (+)-retronecine (**1**) and (+)-crotanecine (**2**), have been synthesised from D-glucose. The salient features of this approach involves the formation of 6,3-epimino ring followed by deoxygenation of unrequired hydroxyl groups via Barton-McCombie deoxygenation method.

The synthesis[1] of pyrrolizidine alkaloids[2], such as retronecine (**1**) and crotanecine (**2**), is a subject of current interest because of several biological activities[3] associated with them. Benn and coworkers[4,5] have recently shown that the optically active synthesis of these alkaloids could be achieved using chiral derivatives (**3** and **4**) of 6-aza-2-oxabicyclo[3.3.0]octan-3-one following essentially the methodology developed by Geissman and Waiss[6]. Compounds **3** and **4** have been obtained from L-4-hydroxyproline. Later Buchanan *et al.*[7] prepared **3** from 2,3-O-isopropylidene-D-erythrose. In this paper we report, starting from D-glucose, the syntheses of compounds **5** and **6** suitable for elaborating these into pyrrolizidine alkaloids **1** and **2**.

Diacetone-D-glucose (**8**) was transformed into 3-azido-3,5-dideoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranose (**10**) via the intermediate (**9**) by a reported procedure[8] (Scheme 1). The mesylate (**11**) of **10** revealed in its PMR spectrum a downfield shift of a triplet due to H-6,6′ by 0.59 ppm, clearly suggesting the presence of mesyloxy group at C-6. Hydrogenation of **11** over Pd/C at normal pressure and temperature led to the amine (**12**) which was immediately subjected to internal cyclisation[9] with sodium acetate in refluxing ethanol. The resulting 6,3-epimine (**13**) was protected as N-acetate (**14**). The PMR spectrum of **14** at room temperature showed doubling of ring proton resonances due to restricted rotation across NCO bond. However, PMR spectrum at higher temperature[9] revealed a clear-cut picture of the assigned structure and doubling of resonances had vanished completely at 80°. Treatment of 14 with dry methanol and Amberlite IR 120 (H) resin under reflux afforded a mixture of isomeric (α and β) methyl glycosides (**15**) whose PMR spectrum was compatible with assigned structure.

Deoxygenation of the hydroxyl group adjacent to the anomeric centre in **15** was difficult by conven-



Scheme 1

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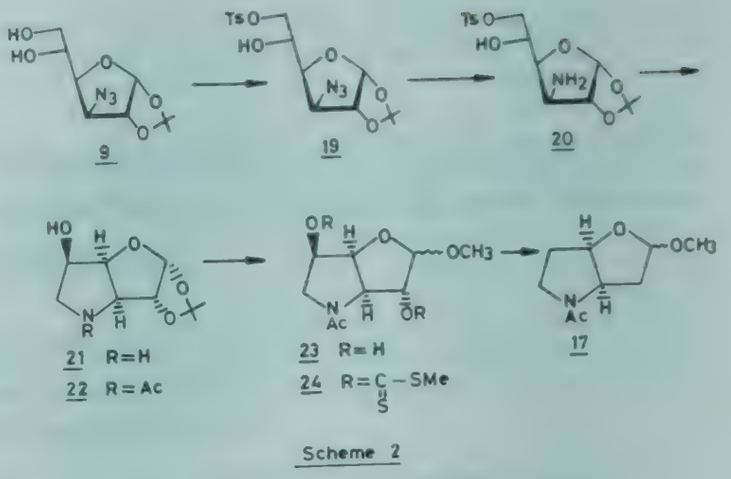
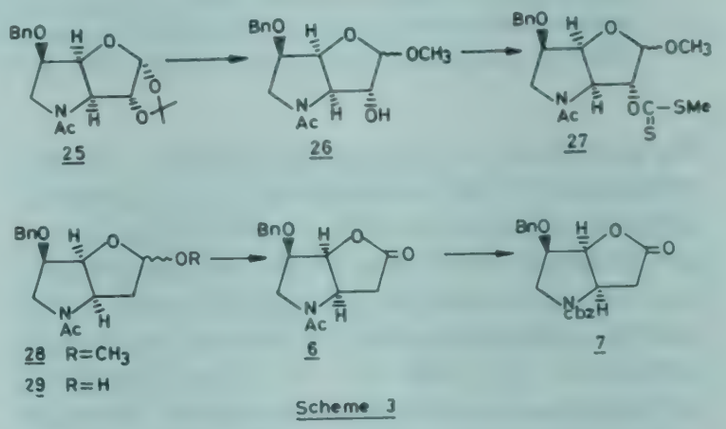
tional procedures. However, barton-McCombie[10] method was found suitable for deoxygenation. Therefore, **15** was first converted into the xanthate derivative **16** which on treatment with tri-*n*-butyltin hydride and α,α′-azoisobisbutyronitrile (AIBN) in refluxing toluene gave the 2-deoxy product (**17**) (Scheme 1). The PMR spectrum of **17** was in agreement with the assigned structure. The loss of S-methyl peak of **16** and appearance of a four-proton multiplet at δ 2.0 were some of the characteristic features of the PMR spectrum of **17**. Compound (**18**) obtained by the hydrolysis of **17** by aqueous acetic acid at 100°, on oxidation with pyridinium chlorochromate in methylene chloride at room temperature afforded the bicyclicactone (**5**) (Scheme 1).

An alternative route to **5** was planned (see Scheme 2) in which the successive deoxygenation of OH groups at C-2 and C-5 was effected by Barton-McCombie procedure. Accordingly, **9** was selectively[11] tosylated at C-6 to afford **19**, the PMR spectrum of which exhibited a singlet for tosyl-methyl group. The minor product obtained in the above reaction was undoubtedly the 5,6-ditosylate, as revealed by its PMR spectrum. Hydrogenation of **19** over 10% Pd/C at normal pressure and temperature gave the amine (**20**) which was cyclised with sodium acetate to give **21**. The free amine group in **21** was selectively protected as N-acetate (**22**)[12] using acetic anhydride and methanol. **22** was heated under reflux with dry methanol and Amberlite IR 120 (H) resin to yield the glycoside (**23**). Treatment of **23** with sodium hydride-carbon disulfide-methyl iodide in tetrahydrofuran furnished the dixanthate (**24**). Although the PMR spectrum of **24** was not amenable to first order analysis, peaks corresponding to two S-methyl groups were clearly visible around δ 2.5. Compound **24**, tri-*n*-butyltin hydride and AIBN were heated under reflux for 8 hr to give the dideoxy derivative (**17**).

In our pursuit to prepare the intermediate **7** suitable for elaborating into crotanecine (**2**), we envisaged the utility of compound **22** (see Scheme 3). Thus, OH in **22** was protected with benzyl group to afford the O-benzyl ether (**25**), which on treatment with dry methanol and acid furnished **26** whose PMR spectrum suggested it to be a α,β-mixture of methyl glycosides. Conversion of **25** into the xanthate derivative (**27**) was achieved by the procedure reported earlier. Deoxygenation of **27** with tri-*n*-butyltin hydride gave **28**. In the PMR spectrum of **28**, a characteristic multiplet for H-2,2′ protons appeared around δ 2.1. Finally **28** was hydrolysed with acetic acid to the hemiacetal (**29**), which on oxidation with PCC at room temperature gave **6**.



Scheme 2



Scheme 3

Compound **6** was converted into N-carbobenzyloxy derivative (**7**) by initial hydrolysis of the N-acetyl group with barium hydroxide followed by conventional carbobenzyloxylation with benzyl chloroformate in aq sodium bicarbonate.

Experimental Procedure

General

Melting points were taken on a Kofler hot plate and are uncorrected. PMR spectra were scanned on Varian 80A-FT or Bruker WH-90 in $CDCl_3$ with TMS as internal standard and IR spectra on Perkin-Elmer instrument. All the solvents were purified and distilled and light petroleum refers to the fraction b.p. 60-80°. All the optical rotations were measured on JASCO DIP 181 polarimeter. Solvents were removed under reduced pressure on Buchii rota evaporator.

3-Azido-3,5-dideoxy-1,2,O-isopropylidene-6-O-methanesulphonyl-α-D-xylo-hexofuranose (**11**)

To a solution of **10** (0.5 g, 2.18 mmol) in dry pyridine (3 ml) was added methanesulphonyl chloride (1 ml, 8.73 mmol) at 0°C, and the reaction mixture was stirred for 1.5 hr at room temperature (TLC monitoring). After completion of reaction the reaction mixture was poured into ice-water, stirred for 0.5 hr, extracted with chloroform, the chloroform layer

washed with 10% aq sodium carbonate, water, dried (sodium sulphate) and concentrated. Traces of pyridine were removed by co-distillation with toluene to afford a residue which was chromatographed on a column of silica gel. Elution with ethyl acetate-light petrol (1:10; 1:1) afforded **11** (0.57 g, 95%), m.p. 93°, $[\alpha]_D$ −34.4° (*c*, 0.7, chloroform); PMR ($CDCl_3$): δ 1.29 and 1.50 (2*s*, 6H, CMe_2), 2.11 (*q*, 2H, H-5,5′), 2.98 (*s*, 3H, O_2SMe), 3.85 (*d*, 1H, *J* = 3.5 Hz, H-3), 4.2-4.45 (*m*,3H, H-4,6,6′), 4.65 (*d*, 1H, *J* = 3.5 Hz, H-2), 5.81 (*d*, 1H, *J* = 3.5 Hz, H-1); IR (film): 2100 cm^{-1} (N_3). MS: *m/z* 292 (M^+-15) (Found: C, 39.2; H, 5.4; N, 13.4. $C_{10}H_{17}N_3O_6S$ requires C, 39.1; H, 5.5; N, 13.6%).

3,6-*Acetylepimino*-3,5,6-*trideoxy*-1,2-*O*-*isopropylidene*-α-D-*xylohexofuranose* (**14**)

Compound **11** (0.57 g, 2 mmol) in methanol (20 ml) was hydrogenated over 10% Pd-C (0.1 g) at atmospheric pressure and room temperature for 18 hr (TLC monitoring). The catalyst was filtered and the filtrate co-concentrated with benzene to obtain 3-amino-3,5-dideoxy-1,2,-O-isopropylidene-6-O-methane-sulphonyl-α-D-xylo-hexofuranose (**12**) (0.49 g, 90%) which was used as such in the next step.

A solution of **12** (0.49 g, 1.96 mmol) in ethanol (17 ml) containing sodium acetate (0.75 g, 9.1 mmol) was heated under reflux for 6 hr (TLC monitoring). The solvent was removed under reduced pressure and the residue extracted several times with hot ethyl acetate. Removal of solvent afforded 3,6-epimino-3,5,6-trideoxy-1,2-O-isopropylidene-D-xylo-hexofuranose (**13**) (0.31 g, 85%).

Compound **13** (0.3 g, 1.62 mmol) was acetylated with acetic anhydride (1 ml, 9.8 mmol) and pyridine (3 ml) at room temperature for 2 hr. Conventional work-up was followed by chromatography over a silica gel column with ethyl acetate-methanol (9:1) as eluant to afford **14** (0.31 g, 81%); m.p. 96°C $[\alpha]_D$-96° (*c*, 0.6, chloroform); PMR ($CDCl_3$): δ 1.30, 1.50 (2*s*, 6H, CMe_2), 2.07 (*s*, 3H, $NCOCH_3$), 1.8-2.3 (*m*, 2H, H-5,5′), 4.8-5.1 (*m*, 2H, H-2,4), 5.75-5.95 (*dd*, 1H, H-1); IR (film): 1645 cm^{-1} ($NCOCH_3$); MS: *m/z* 212 ($M^+ - 15$), 169 ($M^+ - CH_3 - CH_3CO$), 125 ($M^+ - CH_3 - 2CH_3CO$). GC analysis: t_R 4.16 min (OV 101, 200°C) (Found: C, 58.2; H, 7.3; N, 6.0. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.48; N, 6.1%).

Methyl 3,6-*acetylepimino*-3,5,6-*trideoxy*-(α,β)-D-*xylo*-*hexofuranoside* (**15**)

A solution of **14** (0.3 g, 1.32 mmol) was heated under reflux with methanolic Amberlite IR 120 resin for 3 hr. The solution was filtered and the filtrate was concentrated and the residue chromatographed over silica gel column using ethyl acetate-methanol (19:1) as eluent to obtain **15** (0.215 g, 85%) as a syrup; PMR (β-isomer, $CDCl_3$): δ 2.03 (*m*, 5H, $NCOCH_3$ and H-5,5′), 3.30 (*s*, 3H, OMe), 3.14-4.25 (*m*, 4H, H-2,3,6,6′), 4.81 (*s*, 1H, H-1), 4.91 (*m*, 1H, H-4); IR (film): 3200 (OH), 1630 cm^{-1} ($NCOCH_3$); MS: *m/z* 201 (M^+), 169 ($M^+ - MeOH$) (Found: C, 53.4; H, 5.8; N, 6.7. $C_9H_{11}NO_4$ requires C, 53.7; H, 5.47; N, 6.9%).

Methyl 3,6-*acetylepimino*-3,5,6-*trideoxy*-2-*S*-*carbamoyl*-(α,β)-D-*xylo*-*hexofuranoside* (**16**)

To a stirred solution of **15** (0.2 g, 1.01 mmol) in dry tetrahydrofuran (6 ml) was added sodium hydride (50% oil dispersion, 0.2 g, 8.33 mmol) in small portions and under nitrogen. After stirring for 1.5 hr, carbon disulphide (0.6 ml) was added, followed after 20 min by methyl iodide (1.1 g, 7.7 mmol). The reaction mixture was stirred for 4 hr at room temperature. TLC (ethyl acetate) indicated a faster moving product. Methanol (3 ml) was carefully added, the solvent removed under diminished pressure and extracted with chloroform. The chloroform layer was washed with aq sodium thiosulphate, water, dried and subjected to chromatography on a column of silica gel by elution with ethyl acetate to afford **16** as a syrupy compound (0.27 g, 91%); PMR ($CDCl_3$): δ 2.05 (*s*, 3H, $NCOCH_3$), 2.57 (*s*, 3H, SMe), 3.37 (*s*, 3H, OMe), 5.9 (*s*, 1H, H-2); IR (film): 1650 cm^{-1} ($NCOCH_3$): MS: *m/z* 291 (M^+), 259 ($M^+ - MeOH$) (Found: C, 45.2; H, 5.7; N, 4.7. $C_{11}H_{17}NO_4S$ requires C, 45.3; H, 5.8; N, 4.8%).

Methyl 3,6-*acetylepimino*-2,3,5,6-*tetradeoxy*-(α,β)-D-*threo hexofuranoside* (**17**)

To a stirred solution of **16** (0.27 g, 0.92 mmol) in dry toluene (15 ml) and under nitrogen was added tri-*n*-butyltin hydride (1 g, 3.4 mmol) and α,α′-azobisisobutyronitrile (5 mg). The solution was heated under reflux for 8 hr (TLC monitoring) and then concentrated and poured over a dry packed silica gel column. Elution with ethyl acetate-light petrol (1:1) followed by ethyl acetate-methanol (9:1) gave **17** (0.14 g, 82%); PMR ($CDCl_3$, β-isomer): δ 1.6-2.3 (*m*, 4H, H-2,2′,5,5′), 2.00 (*s*, 3H, $NCOCH_3$), 3.25 (*s*, 3H, OMe), 3.4 (*m*, 2H, H-6,6′), 4.45 (*m*, 1H, H-3), 4.71 (*m*, 1H, H-4), 4.93 (*m*, 1H, H-1); IR (film): 1635 cm^{-1} ($NCOCH_3$); MS: *m/z* 185 (M^+), 153 ($M^+ - MeOH$) (Found: C, 58.1; H, 8.0; N, 7.4. $C_9H_{15}NO_3$ requires C, 58.3; H, 8.1; N, 7.5%).

N-*Acetyl*-(1*R*,5*R*)-6-*aza*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (**5**)

A solution of **17** (0.12 g, 0.6 mmol) in aq 50% acetic acid (3 ml) was heated on water-bath for 3 hr

and then concentrated. Traces of acetic acid were removed by co-distillation with toluene. The residue was chromatographed on a column of silica gel. Elution with ethyl acetate-methanol (9:1) gave **18** (0.095 g, 86%).

Compound **18** (0.095 g, 0.55 mmol) in dry methylene chloride (4 ml) was stirred with pyridinium chlorochromate (0.15 g, 0.69 mmol) at room temperature for 20 hr. After addition of dry ether (10 ml) the reaction was transferred over a dry packed column of silica gel. Elution first with ethyl acetate and then with ethyl acetate-methanol (19:1) gave **5** (0.08g, 86%), $[\alpha]_D$ −192° (*c*, 0.4, chloroform); PMR ($CDCl_3$): δ1.6-2.7 (*m*, 2H, H-8,8′), 2.02 (*s*, 3H, $NCOCH_3$), 2.8 (*d*, 2H, H-4,4′), 3.1-3.8 (*m*, 2H, H-7,7′), 4.5 (*m*, 1H, H-5), 5.0 (*m*, 1H, H-1); IR (liq. film): 1780 (γ-lactone), 1630 cm^{-1} ($NCOCH_3$); MS: *m/z* 169 (M^+); GC: R_t 3.25 min (92%, OV 101, 200°C column temperature) (Found: C, 63.7; H, 7.4; N, 8.1. $C_9H_{13}NO_3$ requires C, 63.9; H, 7.6; N, 8.2%).

3-Azido-3-deoxy-6-O-toluene-p-sulphonyl-1,2-O-isopropylidene-α-D-glucofuranose (**19**)

To a stirred solution of **9** (3.4 g, 13.9 mmol) in dry pyridine (25 ml) at 0°C was added toluene-*p*-sulfonyl chloride (3.17g, 16.6 mmol) in small portions. The reaction mixture was stirred overnight at room temperature. TLC (ethyl acetate-light petrol, 1:4) indicated one major and two minor compounds. The reaction mixture was poured over crushed ice, stirred for 0.5 hr and extracted with chloroform. The chloroform layer was washed with aq 10% sodium carbonate, water, dried (sodium sulphate) and concentrated. The residue was co-distilled with toluene till free of pyridine and then chromatographed on a column of silica gel. Elution with ethyl acetate-light petrol (1:4) gave the ditosylate (0.4 g) and then the monotosyl compound **19** (3.4 g, 72%) as a syrup: $[\alpha]_D$ −10.6° (*c* 0.6, chloroform); PMR ($CDCl_3$): δ 1.28, 1.46 (2*s*, 6H, CMe_2), 1.85 (*m*, 1H, OH), 2.44 (*s*, 3H, O_2SAr-Me), 3.85-4.45 (*m*, 5H, H-3,4,5,6,6′), 4.56 (*d*, 1H, $J_{1,2}$ = 3.5 Hz, H-2), 5.75 (*d*, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 7.5 (*q*, 4H, Ar*H*, *J* = 9 Hz and *J* = 28 Hz): IR (liq. film): 3500 (OH), 2100 cm^{-1} (N_3) (Found: C, 48.3; H, 5.2, N, 10.4; S, 8.1. $C_{16}H_{21}N_3O_7S$ requires C, 48.1; H, 5.3; N, 10.5; S, 8.0%).

3,6-Acetylepimino-3,6-dideoxy-1,2-O-isopropylidene-α-D-glucofuranose (**22**)

A solution of **19** (1.45 g, 3.63 mmol) in methanol (30 ml) was hydrogenated over 10% Pd-C (0.26 g) at normal pressure and room temperature for 10 hr. The catalyst was filtered over celite and the filtrate concentrated. The residue was co-distilled with benzene several times to obtain 3-amino-3-deoxy-6-O-toluene-*p*-sulphonyl-α-D-glucofuranose (**20**). The amine **20** was dissolved in ethanol, sodium acetate (2.0 g) added and heated under reflux for 4 hr. The solvent was removed under reduced pressure and the residue extracted with hot ethyl acetate. The ethyl acetate solution was concentrated to obtain 3,6-epimino-3,6-dideoxy-1,2-O-isopropylidene-α-D-glucofuranose **21**, which was treated with acetic anhydride (3 ml) in methanol (10 ml) at room temperature for 2 hr. The solvent was removed and the residue chromatographed on a column of silica gel. Elution with ethyl acetate-methanol (9:1) gave **22** (0.35 g, 42%), crystallised from chloroform-light petrol, m.p. 152°, (lit[12], m.p. 154-55°), $[\alpha]_D$ −84.5° (*c*, 1, chloroform) (lit[12] $[\alpha]_D$ −88.5° (*c*, 1, chloroform).

Methyl 3,6-acetylepimino-3,6-dideoxy-(α,β)-D-glucofuranoside (**23**)

A stirred solution of **22** (0.163 g, 0.67 mmol) in methanol (5 ml) containing Amberlite IR 120 (H^+) resin (0.2 g) was heated under reflux for 6 hr. The resin was filtered, the filtrate concentrated to afford a residue which was chromatographed on a column of silica gel. Elution with ethyl acetate-methanol (9:1) gave **23** as a syrupy liquid (0.11 g, 76%); PMR (β-isomer, $CDCl_3$): δ 1.93 (*s*, 3H, $NCOCH_3$), 3.25 (*s*, 3H, OCH_3), 3.0-3.74 (*m*, H-4, H-6,6′ + 2 OH), 4.96 (*s*, 1H, H-1); IR (liq. film): 3400 (OH), 1645 cm^{-1} ($NCOCH_3$) (Found: C, 49.8; H, 7.0; N, 6.4. $C_9H_{15}NO_5$ requires C, 49.7; H, 6.9; N, 6.4%).

Methyl 3,6-acetylepimino-3,6-dideoxy-2,5-dithiocarbamoyl-(α,β)-D-glucofuranoside (**24**)

To a stirred solution of **23** (0.11 g, 0.51 mmol) in dry tetrahydrofuran (6 ml) was added sodium hydride (0.2 g, 8.33 mmol, 50% oil dispersion) in small portions and under nitrogen. After stirring for 2 hr, carbon disulphide (0.6 ml) was added and after 20 min followed by methyl iodide (1.19 g, 7.9 mmol). The reaction mixture was stirred overnight, methanol carefully added, solution evaporated to dryness and the residue chromatographed on a column of silica gel. Elution with light petrol and then with ethyl acetate-light petrol (2:1) gave a syrupy **24** (0.145 g, 81%); PMR ($CDCl_3$): δ 2.06 (*s*, 3H, $NCOCH_3$), 2.56, 2.64 (2s, 6H, 2 × SMe), 3.42 (*s*, 3H, OCH_3), 5.08 (*s*, 1H, H-1), 5.1-5.9 (*m*, 2H, H-2,5); IR (liq. film): 1650 cm^{-1} ($NCOCH_3$) (Found: C, 39.4; H, 4.9; N, 3.5; S, 32.1. $C_{13}H_{19}NO_5S_4$ requires C, 39.3; H, 4.8; N, 3.5; S, 32.2%).

Methyl 3,6-acetylepimino-2,3,5,6-tetradeoxy-(α,β)-D-threo-hexofuranoside (**17**)

To a stirred solution of **24** (0.145 g, 0.36 mmol) in dry toluene (12 ml) under nitrogen, was added tri-*n*-

butyltin hydride (1 g, 3.4 mmol) and α,α′-azobisisobutyronitrile (5 mg). The solution was heated under reflux for 8 hr. TLC (ethyl acetate-light petrol, 2:1) indicated a slower moving product. The reaction mixture was concentrated and purified on a silica gel column with ethyl acetate-methanol (9:1) as eluant to give **17** (0.055 g, 82%). This compound was identical with the sample prepared earlier.

3,6-Acetylepimino-3,6-dideoxy-5-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (**25**)

To a stirred of **22** (0.35 g, 1.44 mmol) in dry tetrahydrofuran (5 ml) was added sodium hydride (0.176 g, 7.34 mmol, 50% oil dispersion) in small portions under nitrogen. The reaction mixture was stirred for 1.5 hr at room temperature, benzyl bromide (0.3 g, 1.89 mmol) gradually added and the reaction mixture further stirred overnight. TLC (ethyl acetate-methanol, 9:1) indicated a faster moving product. Methanol was carefully added to the reaction mixture, the solvent evaporated to dryness and the residue chromatographed on a column of silica gel. Elution with ethyl acetate-methanol (9:1) gave **25** (0.39 g, 81%), which crystallised from chloroform-light petrol, m.p. 120°C, $[\alpha]_D$ −15.1° (*c*, 0.65, chloroform); PMR ($CDCl_3$): δ 1.31, 1.50 (2*s*, 6H, CMe_2), 2.01 (*s*, 3H, $NCOCH_3$), 3.2-5.0 (*m*, 8H, H-2,3,4,5,6,6′ and CH_2Ph), 5.87 (*dd*, 1H, *J*= 3.5 Hz, H-1), 7.3 (*s*, 5H, Ph): IR (liq. film): 1650 cm^{-1} ($NCOCH_3$): MS: *m/z* 318 ($M^+ - 15$) (Found: C, 65.1; H, 6.8; N, 4.3. $C_{18}H_{23}NO_5$ requires C, 64.9; H, 6.9; N, 4.2%).

Methyl 3,6-acetylepimino-3,6-dideoxy-5-O-benzyl (α,β)-D-glucofuranoside (**26**)

A solution of **25** (0.38 g, 1.14 mmol) in 3% methanolic hydrogen chloride (10 ml) was heated under reflux for 4 hr when TLC (ethyl acetate-methanol (9:1) showed a slower moving product. The solution was neutralised with lead carbonate and filtered through a celite pad and the filtrate concentrated. Column chromatography of the residue over silica gel with ethyl acetate-methanol (9:1) as eluant gave the syrupy **26** (0.310 g, 86%); PMR ($CDCl_3$): δ 1.97 (*s*, 3H, $NCOCH_3$), 2.56 (*bs*, 1H, OH), 3.37 (*s*, 3H, OCH_3), 3.5-4.1 (*m*, 5H, H-3,4,5,6,6′), 4.25 (*s*, 1H, H-2), 4.64 (*q*, 2H, *J*= 12 Hz, CH_2Ph), 4.96 (*s*, 1H, H-1), 7.3 (*s*, 5H, Ph); IR (liq. film): 3380 (OH), 1630 cm^{-1} ($NCOCH_3$). MS: *m/z* 307 (M^+), 275 ($M^+ - 32$) (Found: C, 62.4; H, 6.8; N, 4.57. $C_{16}H_{21}NO_5$ requires C, 62.5; H, 6.8; N, 4.6%).

Methyl 3,6-acetylepimino-3,6-dideoxy-5-O-benzyl-2-S-carbamoyl (α,β)-D-glucofuranoside (**27**)

To a stirred solution of **26** (0.307 g, 1 mmol) in dry tetrahydrofuran (15 ml) was added sodium hydride (0.912 g, 8 mmol, 50% oil dispersion) in small portions, under nitrogen. After stirring for 1.5 hr, carbon disulphide (0.3 ml) was added followed, after 20 min, by methyl iodide (0.44 g, 2.89 mmol). The reaction mixture was stirred for 3.5 hr at room temperature when TLC (ethyl acetate-light petrol, 1:1) showed a faster moving product. Methanol was carefully added, the solution evaporated to dryness and the residue chromatographed on a column of silica gel. Elution with ethyl acetate gave syrupy **27** (0.35 g, 88%); PMR ($CDCl_3$): δ 2.01 (*s*, 3H, $NCOCH_3$), 2.56 (*s*, 3H, SMe), 3.39 (*s*, 3H, OMe), 3.5-5.0 (*m*, 7H, H-3,4,5,6,6′ + CH_2Ph), 5.06 (*s*, 1H, H-1), 5.83 (*s*, 1H, H-2), 7.3 (*s*, 5H, Ph); IR (liq. film): 1645 cm^{-1} ($NCOCH_3$). MS: 397 (M^+) (Found: C, 54.2; H, 5.8; N, 3.6. $C_{18}H_{23}NO_5S_2$ requires C, 54.4; H, 5.8; N, 3.5%).

Methyl 3,6-acetylepimino-2,3,6-trideoxy-5-O-benzyl (α,β)-D-arabino-hexofuranoside (**28**)

To a stirred solution of **27** (0.3 g, 0.75 mmol) in dry toluene (20 ml) under nitrogen, was added tri-*n*-butyltin hydride (1.0 g, 3.4 mmol) and α,α′-azobisisobutyronitrile (5 mg). The solution was heated under reflux for 6 hr when TLC (ethyl acetate) indicated a slower moving product. Solvent was removed under diminished pressure and the residue subjected to column chromatography on silica gel column. Elution with ethyl acetate-methanol (9:1) gave **28** (0.18 g, 82%); PMR ($CDCl_3$) (α-isomer): δ 1.97 (*s*, 3H, $NCOCH_3$), 2.1-2.4 (*m*, 2H, H-2,2′), 3.31 (*s*, 3H, OCH_3), 3.4-4.9 (*m*, 5H, H-3,4,5,6,6′), 4.62 (*q*, 2H, *J*= 12 Hz CH_2Ph), 5.03 (*d*, 1H, *J*= 4.7 Hz, H-1), 7.3 (*s*, 5H, Ph); IR (liq. film): 1645 cm^{-1} ($NCOCH_3$) (Found: C, 66.2; H, 7.2; N, 4.8. $C_{16}H_{21}NO_4$ requires C, 66.0; H, 7.2; N, 4.8%).

N-acetyl-(1S,5R,8R)-8-O-benzyl-6-aza-2-oxabicyclo[3.3.0]octan-3-one (**6**)

A solution of **28** (0.1 g, 0.34 mmol) in aq 50% acetic acid (3 ml) was heated on water-bath for 2.5 hr and then concentrated. Traces of acetic acid were removed by co-distillation with toluene. The resulting residue afforded **29** (0.072 g, 74%).

Compound **29** (0.07 g, 0.25 mmol) in dry methylene chloride (4 ml) was stirred with pyridinium chlorochromate (0.1 g, 0.46 mmol) at room temperature for 16 hr. Dry ether (5 ml) was added to the reaction mixture and then transferred to a dry packed column of silica gel. Elution with ethyl acetate-methanol (19:1) gave **6** (0.055 g, 80%): $[\alpha]_D$ −44.8° (*c*, 2.4, chloroform): PMR ($CDCl_3$): δ 2.01 (*s*, 3H, $NCOCH_3$), 2.5-3.1 (*m*, 2H, H-4,4′), 3.4-3.8 (*m*, 2H, H-7,7′), 4.1 (*m*, 1H, H-8), 4.25-4.7 (*m*, 3H, H-5, CH_2Ph), 4.87 (*m*, 1H, H-1); 7.3 (*s*, 5H, Ph): IR (liq.

film): 1780 cm^{-1} (γ-lactone), 1640 cm^{-1} ($NCOCH_3$): MS: *m/z* 275 (M^+) (Found: C, 65.7; H, 6.2; N, 5.2. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.18; N, 5.1%).

N-Carbobenzyloxy-(1*S*,5*R*,8*R*)-8-*O-benzyl-6-aza-2-oxabicyclo*[3.3.0]*octan-3-one* (7)

Compound **6** (0.2 g, 0.72 mmol), water (3 ml) and barium hydroxide (1 g) were heated under reflux for 17 hr and neutralized by passing carbon dioxide gas. The reaction mixture was filtered and filtrate concentrated. To the residue dissolved in 50% ethanol was added sodium bicarbonate (300 mg) and cooled to 0°. Benzyl chloroformate (0.5 ml) was introduced gradually through syringe. After 3 hr at room temperature, it was concentrated, dissolved in chloroform, washed with water, dried and concentrated. The residue was purified on a column of silica gel. Elution with ethyl acetate-light petroleum (1:1) afforded **7** (0.08 g, 31%) $[\alpha]_D$ −23.5° (*c*, 0.4, chloroform); PMR ($CDCl_3$): δ 2.75 (*m*, 2H, H-4,4′), 3.6 (*m*, 2H, H-7,7′), 4.0 (*m*, 1H, H-8), 4.5 (*m*, 3H, H-5, $PhCH_2$), 4.9 (*m*, 1H, H-1), 5.06 (*s*, 2H, $PhCH_2$), 7.31 (*s*, 10H, 2 × Ph) (Found: C, 68.0; H, 5.5; N, 3.5. $C_{21}H_{21}O_5N$ requires C, 68.6; H, 5.7; N, 3.8%).

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References

1 Chamberlin A R & Chung J Y L, *J org Chem*, **50** (1985) 4425.

2 Robins D J, *Fortshr Chem Org Naturst*, **41** (1982) 115; *Chem Abstr*, **97** (1982) 145074 q.

3 Atal C K, *Lloydia*, **41** (1978) 312.

4 Rueger H & Benn M, *Heterocycles*, **19** (1982) 23.

5 Yadav V K, Rueger H & Benn M, *Heterocycles*, **22** (1984) 2735.

6 Geissman T A & Waiss, *J org Chem*, **27** (1962) 139.

7 Buchanan J G, Singh G & Wightman R H, *Chem Commun*, (1984) 1299.

8 Gurjar M K & Patil V J, *Indian J Chem*, **25B** (1986) 1017.

9 Verheyden J P H, Richardson A C, Bhatt R S, Grant B D, Fitch W L & Moffatt J G, *Pure &Appl Chem*, **50** (1978) 1363.

10 Barton D H R & McCombie, *J chem Soc Perkin Trans* 1, (1975) 1574.

11 Reckendorf Zu W M, *Chem Ber*, **101** (1968) 3802.

12 Brimacombe J S & Mofti A M, *Carbohydrate Res*, **18** (1971) 157.

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Organic Synthesis Using PTC : Part 3—Asymmetric Induction in Epoxidation & Michael Addition Reactions of Chalcone under Phase Transfer Conditions Using Optically Active Solvents

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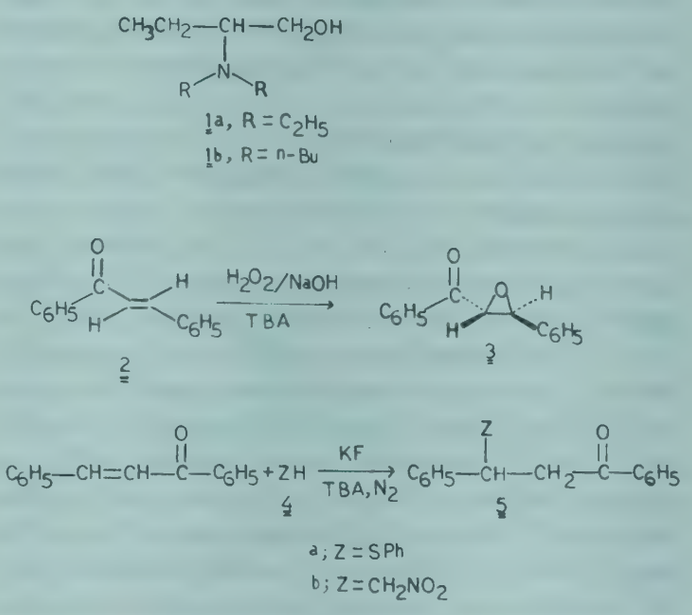
Asymmetric induction in epoxidation and Michael addition reactions of chalcone (**2**) have been performed under phase transfer conditions using optically active solvents as the organic phase and tetrabutylammonium bromide (TBA) as catalyst at ambient temperatures.

Asymmetric induction in prochiral substrates under phase transfer conditions (PTC) has received considerable attention during the last decade or so[1,2]. Optical induction under PTC has been studied in a variety of reactions, viz. borohydride reductions[3], epoxidation[4,5], Michael additions[6], nucleophilic substitutions[7] and alkylation reactions[8]. In all these reactions optically active catalysts derived from quinine, quinidine, ephedine, etc. have been used[2]. These catalysts invariably possess an OH group β to the quaternized nitrogen, considered to be an essential requirement for optical induction[3]. But these catalysts decompose to give oxirane systems under the reaction conditions[9]. The determination of enantiomeric excess (e.e.) in these reactions proved to be abortive. Alternately chiral crown ethers have been used as catalysts, but due to their higher cost their use is not so popular[10]. Recently Julia and coworkers[11] have performed the epoxidation of chalcone in a triphase system and the highest e.e. reported in one case is 96%. To the best of our knowledge the use of optically active solvents in optical induction under PTC is unprecedented in literature. Herein we report the use of optically active solvents in asymmetric induction under PTC.



The optically active solvents 2-(N,N-diethylamino)-1-butanol(**1a**, R = C_2H_5) and 2-(N,N-di-*n*-butylamino)-1-butanol(**1b**, R = *n*-Bu) were prepared from the optically active (−)-2-amino-1-butanol by refluxing it with an appropriate alkyl halide under solid-liquid PTC using benzene as solvent, anhydrous K_2CO_3 as base and tetrabutylammonium bromide (TBA) as catalyst.

Epoxidation of chalcone was carried out by stirring a mixture of chalcone, **1b**, alkaline hydrogen peroxide and TBA as catalyst at room temperature. The epoxide (**3**) obtained after chromatography gave spectral data similar to those reported in literature[12]; $[\alpha]_D^{36}$ −20° (*c*, 2.0, $CHCl_3$). The chalcone epoxide obtained using **1a**, instead of **1b**, as the solvent has an optical rotation of −26° (*c*, 2.0, $CHCl_3$).

In order to investigate the effect of concentration of the optically active solvent on optical induction this reaction was performed using different concenterations of **1a** and **1b** and the results are presented in Table 1.

It is evident from data in Table 1 that as the percentage of optically active solvent decreases, there is decrease in $[\alpha]_D^{36}$ value of the epoxide and hence in optical induction. Secondly, higher $[\alpha]_D$ values have been obtained in **1a** as compared to those in **1b**. This may be attributed to the bulkiness of R group which sterically hinders the formation of hydrogen bond between >C=O of chalcone and −OH of the solvent.

Table 1—Epoxidation of Chalcone under PTC Using Different Concentrations of **1a** and **1b** in Benzene

Optical active solvent (%)	Benzene (%)	Yield (%)	$[\alpha]_D^{36}$	Time (hr)
2-(N,N-di-*n*-butylamino)-1-butanol (**1b**)				
100	0	72	−20°	16
50	50	46	−7.28°	18
25	75	25	−4.5°	20
2-(N,N-diethylamino)-1-butanol (**1a**)				
100	0	55	−26°	10
50	50	35	−9.0°	14
25	75	30	−5.0°	16

In order to see the utility of this methodology, the Michael addition reaction of chalcone has also been investigated under solid-liquid PTC with thiophenol and nitromethane as the Michael donors at room temperature. The reaction of chalcone (**2**) with thiophenol (**4a**) under solid-liquid PTC, in optically active solvent **1b** led to a white solid after 5 min. After chromatography, i.e. purification the solid has an optical rotation $[\alpha]_D^{20}$ of −13.7°. The Michael adduct (**5a**) obtained using **1a** instead of **1b** in the above reaction has an optical rotation, $[\alpha]_D^{20}$ of −20°. The Michael adduct (**5b**) of nitromethane (**4b**, 0.07 mol excess) under above conditions gave the Michael adduct (**5b**) which has optical rotation $[\alpha]_D^{35}$ of +8.8° in optically active solvent **1b**. But as reported earlier e.e. in parent chalcone could not be calculated[13]. The optically active solvents **1a** and **1b** used in these reactions were carefully removed and the products were isolated through column chromatography.

Experimental Procedure

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded on a SP 3-300 spectromom spectrophotometer and PMR spectra on a Jeol 90 MHz instrument. Optical rotations were measured on a Hilger standard polarimeter.

Preparation of 2-(*N,N-diethylamino*)-1-*butanol* (**1a**)

To a solution of 2-amino-1-butanol (8.9g, 0.01 mol) in benzene was added anhydrous potassium carbonate (5g) and catalytic amount of tetrabutylammonium bromide (TBA). Ethyl bromide (21.8g, 0.2 mol) was added slowly to this mixture with stirring and refluxed. The progress of the reaction was followed by TLC. The organic layer was washed with water, dried (Na_2SO_4), solvent removed under reduced pressure and the resulting compound was sufficiently pure; $[\alpha]_D^{35}$ −57.5° (c,2.0, $CHCl_3$), b.p. 150°; PMR ($CDCl_3$): δ1.0(t, 11H, 2×CH_3, CH_2CH_3), 1.4(1H, OH), 2.6(m, 5H, 2×NCH_2, NCH), 3.4(d, 2H, $-CH_2OH$); IR(neat): 3400, 2850, 1470, 1050 cm^{-1}.

2-(*N,N-Di-n-butylamino*)-1-*butanol* (**1b**)

This was prepared as above; $[\alpha]_D^{35}$ −36.5° (c,2.0, $CHCl_3$), b.p. 119-120°; PMR ($CDCl_3$): δ0.95(t, 9H, 3×CH_3), 1.5(m,10H, 5×$-CH_2$-), 2.5(m,4H, 2×$-NCH_2$), 3.1(m, 1H−NCH-), 3.4(m,2H,CH_2-OH);IR $CHCl_3$:3400,2950,1470,1050 cm^{-1}.

General procedure for epoxidation of chalcone (**2**)

To a solution of chalcone 1.04g, 0.005 mol) in **1a** (20 ml) was added a solution (10 ml) of sodium hydroxide in 30% H_2O_2 (0.08g/1 ml). The reaction mixture was stirred at room temperature for the appropriate period (see Table 1). The progress of the reaction was monitored by TLC. A white solid separated out which was dissolved in dichloromethane, the organic layer separated, washed with water and dried (Na_2SO_4). The solvent was distilled off and the residue chromatographed over silica gel to give the epoxide (**3**), identical (m.m.p, co-TLC) with authentic sample. The reaction was performed using **1a** as solvent.

Michael addition of thiophenol (**4a**) *to chalcone* (**2**)

To a solution of chalcone (1.04g, 0.005 mol) in **1b** (20 ml) was added under N_2,KF (0.435g, 0.0075 mol) and catalytic amount of TBA. To this was added thiophenol (0.55g, 0.005 mol) slowly under N_2. The reaction mixture solidified after 5 min. It was dissolved in benzene, washed with water and dried (Na_2SO_4). The solvent was distilled off and the residue was chromatographed over silica gel to give the Michael adduct (**5a**), identical (m.m.p.,, co-TLC) with an anthentic sample, yield 78%; $[\alpha]_D^{20}$ −13.7 (c,0.8,$CHCl_3$). Similar experiment was performed using **1a** as solvent and Michael adduct isolated; yield 70%; $[\alpha]_D^{20}$ −20° (c,0.8,$CHCl_3$).

Michael addition of nitromethane to chalcone (**2**)

To the solution of chalcone (1.04 g, 0.005 mol) in **1b** was added KF (0.435g, 0.0075 mol) and TBA under N_2. To this was added nitromethane (4.57g, 0.0075 mol) and the reaction mixture stirred at room temperature under N_2. The progress of the reaction was followed by TLC. The reaction mixture was extracted with benzene after 48 hr, the organic layer washed with water and dried (Na_2SO_4). The solvent distilled off and the residue was chromatographed over silica gel to give the Michael adduct (**5b**), yield 39%; $[\alpha]_D^{36}$ 8.8° (c,1.34, $CHCl_3$). It was found identical (m.m.p., co-TLC) with an authentic sample.

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References

1 Wynberg H, *Chimica*, **30** (1976) 445.
2 Dehmlow E V & Dehmlow S S, *Phase transfer catalysis* (Verlag Chemie, Weinheim), 1981.
3 Colonna S & Fornasier R, *J chem Soc Perkin Trans-I*, (1978) 371 and references therein.
4 Helder R, Hummelen J C, Laane R W P M, Weiring J S & Wynberg H, *Tetrahedron Lett*, (1976) 1831.
5 Colonna S, Fornasier R & Pfeiffer U, *J chem Soc Perkin Trans-I*, (1978) 8.
6 (a) Colonna S, Albert Re & Wynberg H, *J chem Soc Perkin Trans-I*, (1981) 547 and references therein.
(b) Annunziata R, Cinqeini M & Colonna S, *Chemy Ind*, (1980) 238.
7 Julia S, Ginebreda A, Guixer J & Tomas A, *Tetrahedron Lett*, (1980) 3709.
8 Fiaud J C, *Tetrahedron Lett*, (1975), 3495.
9 Dehmlow E V, Singh P & Joachim J R, *J chem Res(S)*, (1981) 292.
10 Shida Y, Anodo N, Yamamoto Y, Oda J & Inouye Y, *Agric Biol Chem*, **43** (1979) 1797.
11 Banfi S, Colonna S, Molinari H, Julio S & Guixer J, *Tetrahedron Lett*, **40** (1984) 5207.
12 Mitsui S, Senda Y, Shimodaira T & Ichikawa H, *Bull chem Soc Japan*, **38** (1965) 1897.
13 Harada K, *J org Chem*, **81** (1966) 1407.

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A Convenient Synthesis of Thymopentin

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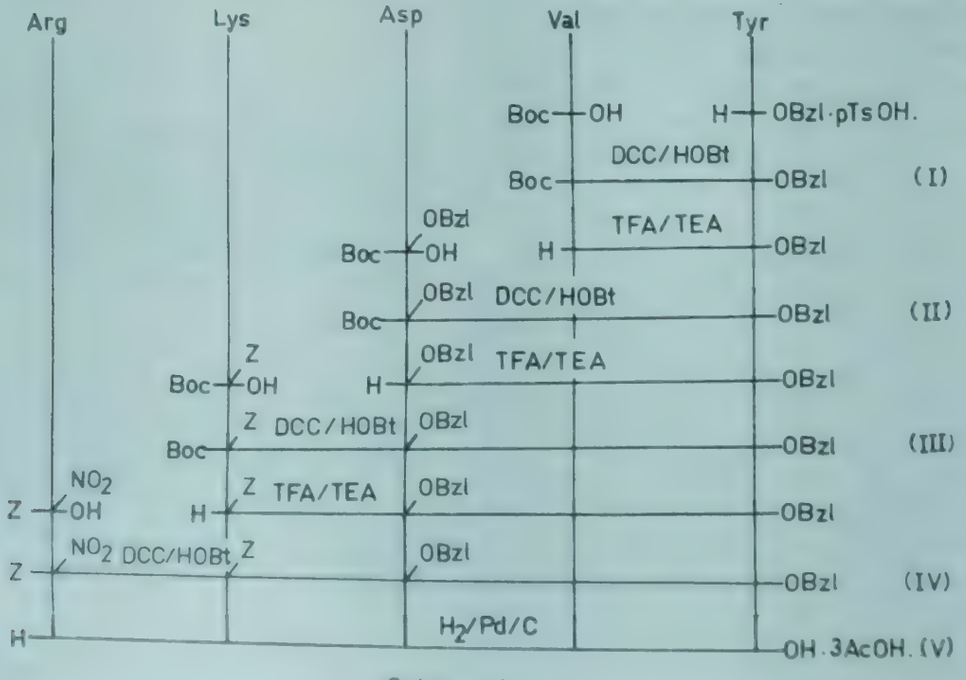
A convenient and economical solution phase synthesis of thymopentin in which the side chain of tyrosine is left unprotected is reported.

Thymopoietin is a 49-amino acid polypeptide hormone of the thymus which regulates neuromuscular transmission[1,2], induces early T-cell differentiation[3] and exerts immunoregulatory effects on peripheral T-cells. The pentapeptide, Arg-Lys-Asp-Val-Tyr, termed thymopentin (TP-5) is being further explored as a therapeutic immunoregulatory agent in human disease and has earlier been synthesised in solid phase[5] and in solution[6,7]. In this paper we describe a convenient and economically viable, large scale preparation of TP-5.

In all the earlier syntheses[5–7], the C-terminal tyrosine was protected in its side chain by a benzyl[8] or substituted benzyl[9,10] groups. Benzyl-based protection of tyrosine hydroxyl, although commonly used, is not entirely satisfactory[9]. The Fmoc group or non-benzyl based protecting groups for tyrosine hydroxyl may be used but such derivatives are quite expensive. In order to economise we planned to introduce tyrosine unprotected in its side chain. This means that reactive intermediates like mixed anhydrides could not be used for coupling reactions. However, we found that DCCI/HOBt mediated couplings at all stages gave excellent results without any side reactions.

The protected pentapeptide (IV) was prepared according to the scheme outlined in Scheme 1. All the protected amino acid derivatives were prepared by published procedures[11]. The dipeptide, Boc-Val-Tyr-OBzl (I), was obtained in 95% yield by DCCI-HOBt mediated coupling. The Boc-group was removed with anhyd. trifluoroacetic acid in dichloromethane and the partially deprotected dipeptide was coupled with Boc-Asp (OBzl) −OH. All other couplings were done in a similar fashion. When arginine was introduced with guanidino group unprotected, the reaction remained incomplete, also giving rise to several side products. It was found suitable to incorporate arginine with its side chain protected with nitro group. Final deprotection of the protected pentapeptide was effected by catalytic hydrogenation (10% Pd-C) to give an almost pure pro-



Scheme 1

duct which was further purified by passing through a bio-gel P-2 column. Removal of the nitro group from IV by catalytic hydrogenation was remarkably smooth; a reaction which often gives side products[12]. The identity and homogeneity of synthetic compound was established by amino acid analysis and reverse phase HPLC. The above procedure was used to make upto 10 g of the protected TP-5 which showed all the characteristics of natural compound.

Experimental procedure

All the optically active amino acids used were of L-configuration. Melting points were taken on Kofler hot bench melting point apparatus and are uncorrected. Amino aids, dicyclohexylcarbodiimide (DCC), 1-hydroxybenztriazole, di-*t*-butyl dicarbonate and trifluoracetic acid (TFA) were commercial products. Triethylamine was distilled over *p*-toluenesulphonyl chloride. Homogeneity of the peptides and amino acid derivatives was established by TLC on silica gel-G plates using three solvent systems : (A) Bu^nOH-AcOH-H_2O (4:1:1); (B) $CHCl_3$-CH_3OH (9:1) and (C) Bu^nOH- pyridine-AcOH-H_2O (4:1:1:2).

The purity of intermediates and final products was also ascertained by HPLC (DU-Pont 8800) using reverse phase column (C_{18}, 4.6 mm × 30 cm) and a methanol-water gradient. Structures of all peptide intermediates were confirmed by PMR spectroscopy. Amino acid analyses were carried out on amino acid analyser LKB Biochem-4150, after usual acid hydrolysis.

Z-Arg (NO_2) – OH, Boc-Asp(OBzl) – OH, Boc-Lys(Z) – OH, Boc-Val-OH and H-Tyr-OBzl.*p*-ToSH were prepared by standard procedures[11] and fully characterised.

N^{α}-t-Butoxycarbonyl-L-valyl-L-tyrosine benzyl ester (I)

A mixture containing *t*-butoxycarbonyl-L-valine (4.3 g, 0.022 mol), HOBt (2.7 g, 0.02 mol), $CHCl_3$ (50 ml) was cooled to 0-5°C in an ice bath and stirred with DCC (4.2 g, 0.022 mol) for 15 min. To this was added a mixture of L-tyrosine benzyl ester, *p*-toluene sulphonate (10.0 g, 0.022 mol), triethylamine (3.0 g, 0.022 mol) in $CHCl_3$ (25 ml) and the resultant mixture stirred for 6 hr. The precipitated dicyclohexylurea was filtered and the filterate was washed successively with 10% citric acid, 5% aq. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated with hexane to give a white solid which was crystallised from EtOAc-hexane; yield 9.0 g (95%), m.p. 89-90°; R_f (A) 0.73; R_f (B) 0.67; (Found: C, 67.0; H, 7.3. $C_{26}H_{34}N_2O_6$ requires C, 66.4; H, 7.2%).

N^{α}-t-Butoxycarbonyl-β-benzyl-L-aspartyl-L-valyl-L-tyrosine benzyl ester (II)

A mixture of *t*-butoxycarbonyl-L-aspartic acid β-benzyl ester (6.4 g, 0.02 mol), HOBt (2.7 g, 0.02 mol) and DCC (4.1 g, 0.02 mol) in dichloromethane (30 ml) was stirred at 0°C for 15 min. The dipeptide (I) (9 g, 0.02 mol) was treated with TFA in dichloroethane (10 ml, 1:1 vol) at 0°C for 45 min, concentrated under reduced pressure and triturated with dry ether several times to give a white solid. This white solid alongwith triethylamine (2.7 ml, 0.02 mol) was added to the above stirred solution, and the reaction was continued overnight. The precipitated dicyclohexylurea was filtered off and the organic filtrate was washed successively with 10% citric acid, 10% aq $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded (II) as a solid which was recrystallised from EtOAc-petroleum ether; yield 8.15 g (62%); m.p. 75-76°; R_f (A) 0.88; R_f (B) 0.8; R_f (C) 0.86; (Found: C, 65.2; H, 6.6. $C_{37}H_{45}N_3O_9$ requires C, 65.8; H, 6.7%).

N^{α}-t-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-β-benzyl-L-aspartyl-L-valyl-L-tyrosine benzyl ester (III)

N^{α}-*t*-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine (4.5 g, 0.012 mol) HOBt (1.62 g, 0.012 mol) and DCC (2.47 g, 0.012 mol) were taken in dichloromethane and the mixture was stirred for 15 min at 0°C. The tripeptide (II) (8.0 g, 0.012 mol) was deprotected using TFA in dichloromethane as earlier, the TFA salt along with triethylamine (2.0 ml, 0.012 mol) was added to the above solution and the mixture stirred at room temperature for 20 hr. The protected tetrapeptide (III) was isolated as in previous case and recrystallised from $CHCl_3$-pet.ether; yield 10.0 g (90%), m.p. 80-81° R_f (A) 0.71; R_f (B) 0.6; R_f (C) 0.76; (Found: C, 65.4; H, 6.8. $C_{51}H_{63}N_5O_{11}$ requires C, 65.3; H, 6.7%).

N^{α}-Benzyloxycarbonyl-N^{ω}-nitro-L-arginyl-N^{α}-benzyloxycarbonyl-L-lysyl-β-benzyl-L-aspartyl-L-valyl-L-tyrosine benzyl ester (IV)

A mixture containing N^{α}-benzyloxycarbonyl-N^{ω}-nitro-L-arginine (0.76 g, 0.0021 mol) and 1-hydroxybenzotriazole (0.28 g, 0.0021 mol) in dichloromethane (10ml) was stirred with DCC (0.28 g, 0.0021 mol) for 15 min at 0°C. The tetrapeptide (III) (1.96 g, 0.0021 mol) was deprotected using TFA in dichloromethane as earlier and the TFA sald along with triethylamine (0.3 ml, 0.0021 mol) was added

to the above solution and the mixture stirred at room temperature for 8 hr. The protected pentapeptide (IV) was isolated and recrystallised from $CHCl_3$-pet.ether; yield 1.9 g (79.1%), m.p. 105-106°, R_f (A) 0.74; R_f (C) 0.68; (Found: C, 61.3; H, 6.1. $C_{60}H_{72}N_{10}O_{15}$ requires C, 61.5; H, 6.0%).

L-Arginyl-L-lysyl-L-aspartyl-L-valyl-L-tyrosine triacetate (V)

The protected pentapeptide (IV) (250 mg) was dissolved in methanol – acetic acid (9:1) (50 ml) and to this was added 10% Pd-charcoal catalyst (80 mg) and hydrogen gas was bubbled slowly for 16 hr. The catalyst was filtered through celite and washed repeatedly with methanol and the combined filtrate was evaporated. The crude peptide was purified on biogel P-2 column (2 × 46.5 cm) using water as eluent. Appropriate fractions (Sakaguchi positive) were pooled and lypholised to obtain (V), yield 165 mg (91%). R_f (A) 0.40; R_f (C) 0.45. Amino acid analysis: Arg (0.98), Lys (1.00), Asp (1.02), Val (0.97), Tyr (0.95).

References

1 Goldstein G, *Nature (London)*, **247** (1974) 11.
2 Hoffman W W & Goldstein G, *clin exptl Immunol*, **4** (1969) 181.
3 Basch R S & Goldstein G, *Proc Natl Acad Sci USA*, **71** (1974) 1474.
4 Goldstein G, Scheid M P, Boyse E A, Schlesinger D H, *Science*, **204** (1979) 309.
5 Rampold G, Voelter W, Kalbachar H & Folkers K, *Z Naturforsch*, **35b** (1980) 1476.
6 Heinzel W, Voelter W & Kronbach T, *Z Naturforsch*, **37b** (1982) 1652.
7 Heavner *et al.*, *Tetrahedron Lett*, **23(43)** (1982) 4439.
8 Wunsch E, Freis G & Zwick A, *Chem Ber*, **91** (1958) 542.
9 Erickson B W & Merrifield R B, *J Am chem Soc*, **95** (1973) 3751.
10 Yamashiro D & Li C H, *Int J Pep Protein Res*, **4** (1972) 181.
11 Fletcher G A & Jones J H, *Int J Peptide Protein Res*, **4** (1972) 347.
12 Iselin B M, in *Peptides*, edited by L Zervas (Pergamon, Oxford), 1966, 27.

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Formation of Quinazolones & Quinolones from Dimethylsulfoxonium-2-(methylamino)benzoylmethylide†

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The mechanism of formation of quinazolones and quinolones in the reaction of title ylid with isothiocyanates is discussed and compared with the mechanism of other reactions of the title ylid and dimethylsulfoxoniummethylide. The mass spectral fragmentations of the above compounds are discussed.

Van Leusen and Taylor[1] have prepared dimethylsulfoxonium-2-(methylamino)benzoylmethylide (**1**) by the reaction of N-methylisatoic anhydride with dimethylsulfoxoniummethylide. it is an acyl-stabilised ylid useful for heterocyclic synthesis as exemplified by the preparation of 1-methyl-2-mercapto-4(1*H*)-quinolone (**2**) by addition of carbon disulfide. The formation of **2** has been rationalised as the nucleophilic addition of either the methylamino group (path-a) or the ylid carbon (path-b) to carbon disulfide, followed by ring closure, transfer of one of the dimethylsulfoxoniummethyl groups to sulphur S and loss of dimethyl disulfide S-oxide as shown in mechanism (A). No conclusions could be drawn as to whether the reaction proceeded by path-a or path-b to give the final product, as *a priori* there were no criteria to judge the relative nucleophilicities of the ylid carbon and the methylamino group. We are outlining in the sequel the results obtained on the addition of a few aryl and aralkyl isothiocyanates and allyl isothiocyanate to **1**.

Reaction of **1** with phenyl isothiocyanate gave in good yield 1-methyl-3-phenyl-2-thioquinazoline-2, 4(1*H*,3*H*)-dione (**3**) described by earlier workers[2], the identity of **3** being confirmed by direct comparison with authentic **3** obtained in the reaction of N-methylisatoic anhydride with phenylthiourea, as described by Kappe[3]. Starting from **1**, analogous products **4** and **5** were obtained by reaction with allyl isothiocyanate and *p*-nitrophenyl isothiocyanate respectively. Reaction of **1** with *p*-phenylene bisisothiocyanate led to *p*-isothiocyanatoquinazolone (**6**) and *p*-phenylene bisquinazolone (**7**). (Table 1). The formation of **3-7** can be visualised as the addition of the isothiocyanate to methylamino group and cyclisation to form the quinazolone with loss of dimethylsulfoxoniummethylide as shown in mechanism (B), path-a. In the case of benzyl isothiocyanate a mixture of products—the quinazolone (**8**) by mechanism (B) and the quinolone (**9**) by mechanism (A)—were obtained. The quinolone (**9**) exhibited in its IR spectrum a band at 1625 cm^{-1} characteristic of 4-quinolones[1].

Van Leusen and Taylor have shown that treatment of **1** with acid resulted in the formation of **10** by protonation and loss of dimethyl sulfoxide as shown in mechanism (B), path (b). The formation of 3-hydroxy-2,3-dihydrobenzofuran (**12**) from salicylaldehyde and dimethylsulfoxoniummethylide is rationalised by the addition of the ylid carbon to the carbonyl function followed by ring closure with elimination of dimethyl sulfoxide on lines similar to mechanism (B)[5]. The fact that no compound corresponding to structure (**11**) is obtained on reaction of **1** with isothiocyanates is indicative of the higher nucleophilicity of the methylamino grouping relative to that of the ylid carbon in **1**.

The mass spectra of 3-aryl-1-methyl-2-thioquinazoline-2, 4(1*H*,3*H*)-diones showed their respective molecular ion peaks along with peaks at *m/z* 159, 134, 132, 105 and 104. The peak at *m/z* 159 can be attributed to species (*a*) arising from the loss of −SH and aryl group from the molecular ion (Scheme 1). The species (*b-e*) can be rationalised as arising from a retro Diels-Alder reaction involving loss of element of aryl isothiocyanate. The above fragmentation pattern bears resemblance to that of the alkaloid arborine[6].

The allyl analogue (**4**) and benzyl analogue (**8**) showed in their mass spectra peaks at *m/z* 160 (*f*) corresponding to loss of CS and vinyl in the case of **4** and CS and benzyl in case of **8**. In the case of quinolone (**9**) peak at *m/z* 159 can be attributed to species (*q*).

The fragmentation pattern of 3-phenyl-2-thioquinazoline 2,4(1*H*,3*H*)-dione[2] is different from

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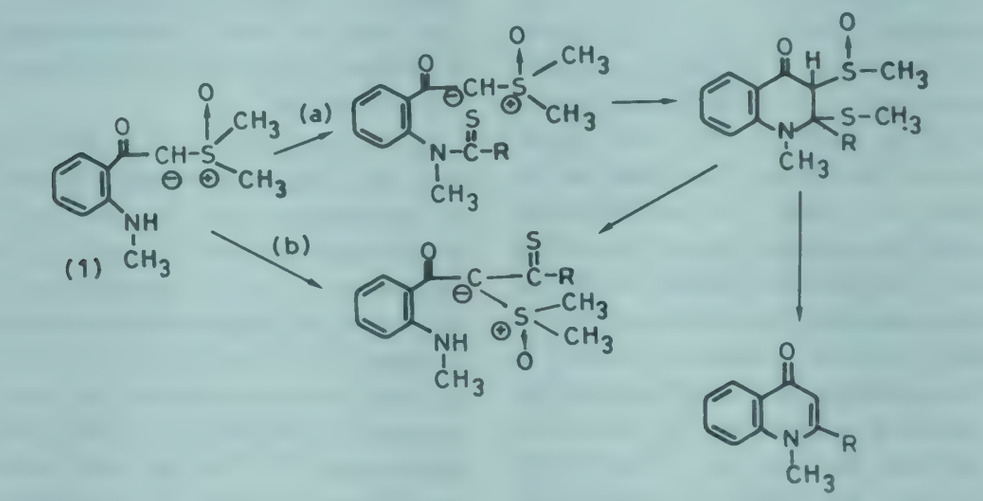
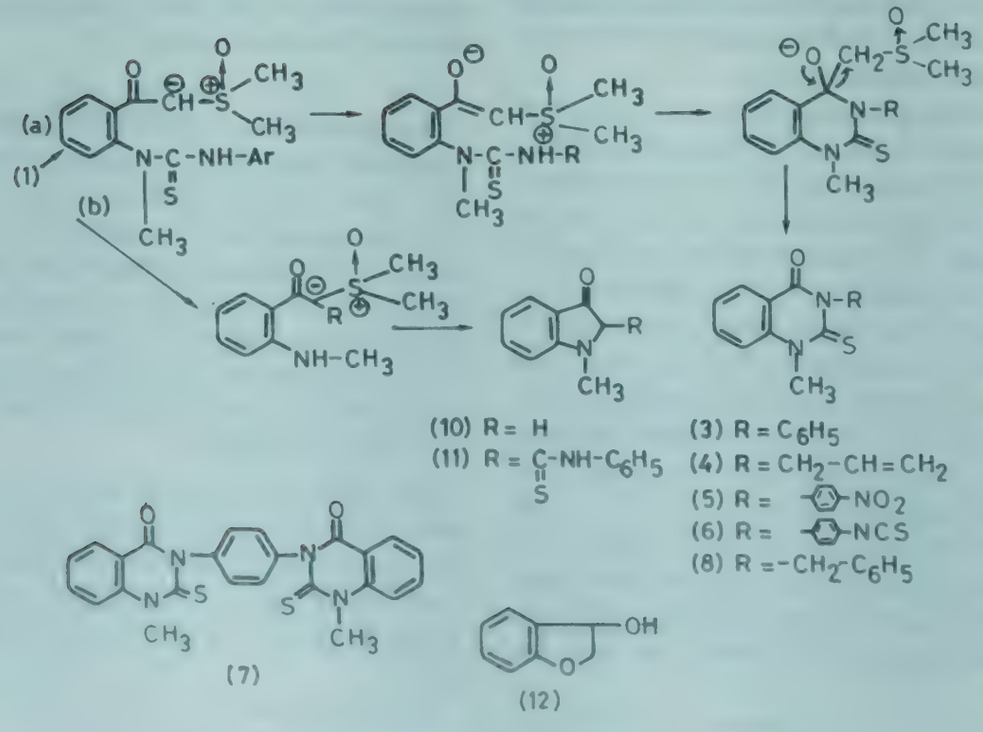
Table 1—3-Aryl(allyl)-1-methyl-2-thioquinazoline-2,4(1*H*,3*H*)-diones

Compd	Solvent of crystallisation	Yield (%)	m.p. (°C)	Found (%) (Calc.)			M⁺
				C	H	N	
3	DMF-isopropanol	54	300 (302-3)	66.9 (67.2)	4.7 (4.5)	10.5 (10.4)	268 (268.26)
4	Benzene-hexane	22	154-56	62.3 (62.1)	5.4 (5.2)	11.9 (12.1)	232 (232.23)
5	DMF-isopropanol	58	292-93	57.4 (57.5)	3.6 (3.5)	13.2 (13.4)	313 (313.26)
6	DMF-H_2O	49	175-76	59.3 (59.1)	3.5 (3.4)	12.9 (12.9)	325 (325.27)
7	DMF	30.5	320	62.8 (62.9)	3.7 (4.0)	12.1 (12.2)	458 (458.42)
8	Methanol	36.5	134	67.9 (68.1)	5.2 (5.0)	10.2 (9.9)	282 (282.29)



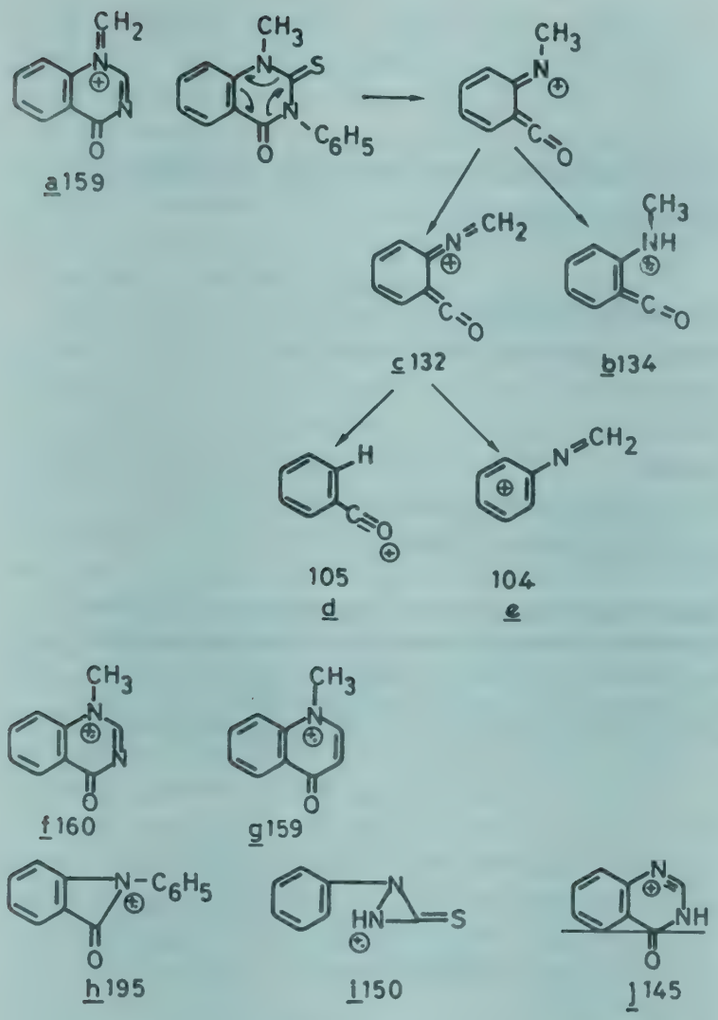
(2) R = SH
(9) R = $NHCH_2$-C_6H_5

Mechanism (A)



(10) R = H
(11) R = C(=S)-NH-C_6H_5
(3) R = C_6H_5
(4) R = CH_2-CH=CH_2
(5) R = p-NO_2-C_6H_4
(6) R = p-NCS-C_6H_4
(8) R = $-CH_2-C_6H_5$

Mechanism (B)



Scheme 1

that of its 1-methyl analogue as shown by the peaks at *m/z* 195, 150 and 145 corresponding to species (*h*), (*i*) and (*j*).

Experimental Procedure

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded in nujol on a Perkin-Elmer model 421 spectrophotometer, UV spectra in 95% ethanol on a Beckman model DK-2A spectrometer and mass specra on a Varian Mat CH_7 mass spectrometer operating at 70 eV.

Reactions of dimethylsulfoxonium 2-(methylamino)-benzoylmethylide (**1**) *with isothiocyanates*: (*a*) *With aryl and allyl isothiocyanates—General method*

A solution of aryl (allyl) isothiocyanate (0.1 mol) in toluene (40 ml) was added to the ylide (**1**) (0.1 mol) in toluene (100 ml) and the reaction mixture heated under reflux under N_2 atmosphere for 4 hr and then cooled. The precipitate was filtered and recrystallized from the appropriate solvent. IR: 1690-1680 cm^{-1}; UV: 292 nm log ε 4.32.

(*b*) *With benzyl isothiocyanate*: *Formation of quinolines* (**8**) *and* **9**

A solution of benzyl isothiocyanate (4.47 g; 0.03 mol) in toluene (15 ml) was added to a solution of **1** (6.78 g; 0.03 mol) in toluene (25 ml) and refluxed for 5 hr. After cooling, the precipitate obtained was filtered to give **9** (0.4 g; 4.5%), m.p. 240° (from methanol); IR: 1625 cm^{-1}; UV: 308 (log ε 4.13), 246 (4.39), 236 (4.46) and 226 nm (4.48) (Found: C, 77.1; H, 6.3; N, 10.3; M^+, 264. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6; M^+, 264.31).

The filtrate was concentrated *in vacuo* and triturated with methylene chloride-hexane to give the quinazolone (**8**) (2.8 g, 36.5%), m.p. 134° (from methanol).

Reaction with p-phenylene isothiocyanate: *Formation of p-phenylenebisquinazolone* (**7**) *and quinazolone* (**6**)

To a solution of *p*-phenylene isothiocyanate (3.84 g; 0.02 mol) in toluene (30 ml) was added dropwise a solution of **1** (4.52 g; 0.02 mol) in toluene (20 ml) and refluxed for 4 hr. The precipitate was filtered and recrystallised from dimethyl formamide to afford pure **7** (2.8 g; 30.4%), m.p. ≥ 320°.

The filtrate was evaporated to give a gummy mass which on treatment with isopropanol gave **6** (3.2 g; 49.1%), *m.p.* 175-76° (from aq. DMF).

References

1 Van Leusen A M & Taylor E C, *J org Chem*, **33** (1968) 66.

2 McCarty J E, Haines E L & Vanderwerf C A, *J Am chem Soc*, **82** (1960) 964.

3 Kappe Th, Steiger W & Ziegler E, *Mh Chem*, **98** (1967) 214.

4 Maillard J, Vincent M, Benard M, Vo-Van-Tri, Jollys R, Morin R, Menillet C & Benharkate, *Chim Ther*, **3** (1968) 100; *Chem Abstr*, **69** (1968) 34529.

5 Holt B & Lowe P A, *Tetrahedron Lett*, (1966) 683.

6 Budzikiewic H, Djerassi C & Williams D H, *Structural elucidation of natural products by mass spectrometry*, Vol. I (Holden-Day, San Francisco), 1964, pp. 212.

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Reactions of Cyclic Anhydrides with Thiosemicarbazide: Synthesis of Fused Heterocyclic Systems

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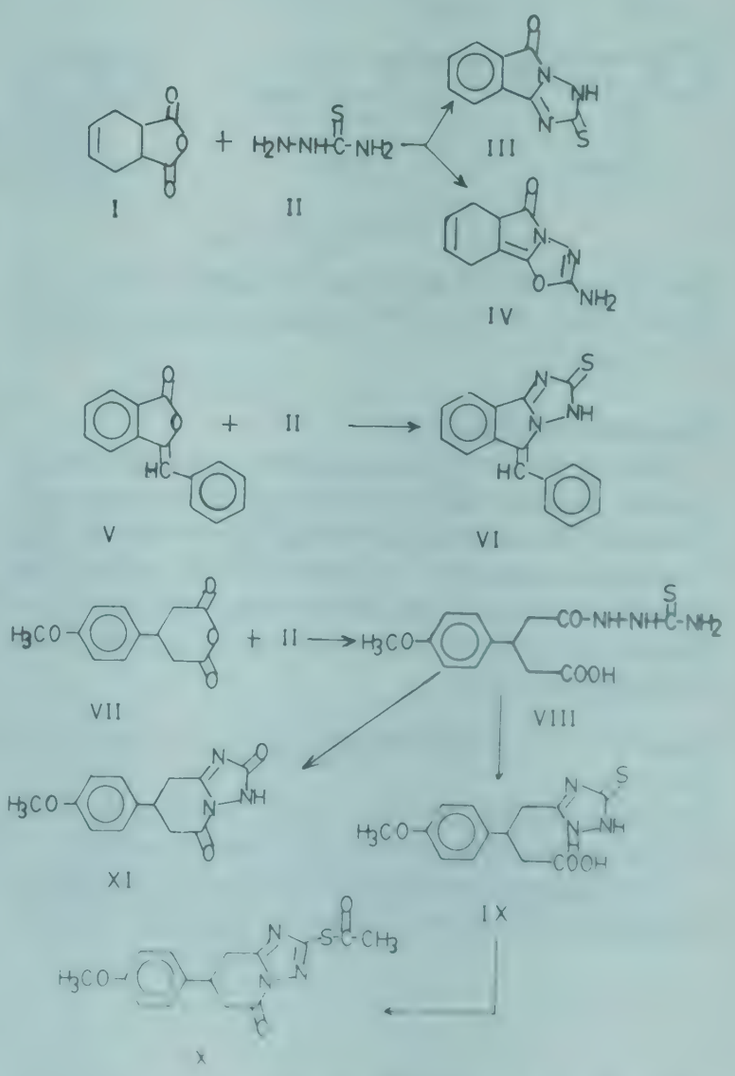
Thiosemicarbazide reacts with cyclic anhydrides such as tetrahydrophthalic anhydride (I), benzalphthalide (V), β-(4-methoxyphenyl)glutaric anhydride (VII), 5-(4-chlorophenylhydrazono)-4-(4-methoxyphenyl)glutaconic anhydride (XII) and α-acetylhomophthalic anhydride (XIV) under different conditions to furnish a variety of fused heterocyclic systems like triazoloisoindoles (III and VI), oxadiazoloisoindole (IV), [1,2,4]triazole (IX), triazolopiperidines (X and XI) and triazoloisoquinoline (XV). The compounds have been characterised on the basis of elemental analyses and spectral (IR, PMR) data.

In continuation of our work on the synthesis of nitrogen hetrocycles, mainly from cyclic anhydrides, we report herein the reactions of some cyclic anhydrides with thiosemicarbazide. We have also used some cyclic anhydrides with reactive functionality at their α-position with respect to the anhydride carbonyl group to study the effect of this on the course of the reaction.

The reaction of tetrahydrophthalic anhydride(I) with thiosemicarbazide(II) did not take place when the mixture was refluxed in dry benzene. However, when the reaction was carried out in dimethylformamide cycloaddition reaction took place to furnish triazoloisoindole(III). The same product was also obtained when the mixture of I and II was fused at 155-160°. The same reaction when carried out in dimethylformamide using fused sodium acetate, cycloaddition reaction took a different course and yielded oxadiazoloisoindole(IV) with expulsion of H_2S. Similarly, the reaction of benzalphthalide(V) with II by heating in gl. acetic acid or on fusion yielded fused heterocyclic system 5-benzylidene-[1,2,4]triazolo[5,7-*a*]isoindole(VI).

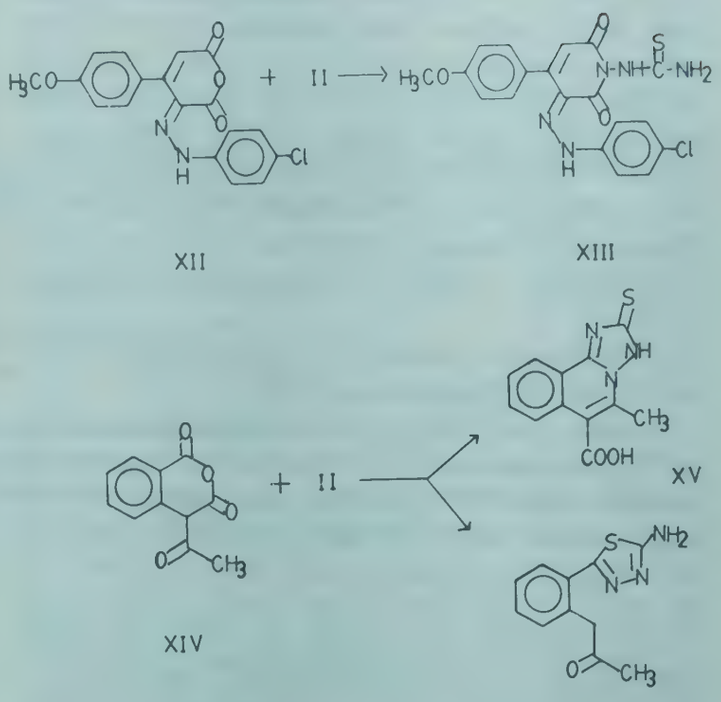
Reaction of II with β-(4-methoxyphenyl)glutaric anhydride (VII) in dry benzene resulted in opening of the anhydride ring to give semianilide VIII, which on heating with sodium hydroxide (5%) underwent intramolecular cyclisation to furnish the triazole system (IX) containing a free carboxy group. This carboxy group was involved in cyclisation with triazole ring when IX was heated with acetic anhydride resulting in the formation of triazolopiperidine system, with simultaneous acetylation of the thiol to give X. However, similar reaction of VIII in acetic anhydride yielded XI, where the thiono group got converted into a carbonyl group.



The reaction of β-(4-methoxyphenyl)glutaconic anhydride with II has already been studied[1]. However, we thought it interesting to study the course of similar reaction by using α-substituted cyclic anhydrides. Reactive functionalities such as acetyl and hydrazo have been incorporated at α-position making use of the reactivity of methylene group in glutaconic anhydride and homophthalic anhydride.

The α-hydrazonoglutaconic anhydride(XII), obtained from glutaconic anhydride by diazocoupling reaction, when heated with II at high temperature gave the imide XIII, whereas α-acetylhomophthalic anhydride(XIV), obtained by acetylation of homophthalic anhydride, underwent simultaneous condensation and cycloaddition with II in dry benzene to give [1,2,4]triazolo[5,1-*a*]isoquinoline (XV). After opening of the anhydride ring it underwent rearrangement where acetyl group took part in cycloaddition to form the fused ring system. The α-acetylglutaconic anhydride on treatment with II under similar conditions as mentioned above gave a mixture of products, which could not be resolved.

Structures III, VI, IX and XV can exist in tautomeric forms, but the thione forms were found to be predominant on the basis of spectral analysis which is in consonance with the literature reports[1–4]. The IR spectra of these compounds displayed bands in the region 1250-1070 cm^{-1} (C=S); bands due to S-H function in the region 2600-2500 cm^{-1} were absent. A sharp band at 1200-1150 cm^{-1} was characteristic of [1,2,4]triazolines[5] in these compounds.



Experimental Procedure

All the m.ps are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Beckmann Acculab-1 and Perkin-Elmer 577 grating instruments and PMR spectra on a Varian EM-360L and Perkin Elmer R-32 instruments using TMS as internal standard (chemical shifts in δ, ppm).

2H,5H-2-thioxo[1,2,4]*triazolo*[5,1-*a*]*isoindol-5-one* (III)

A mixture of I (1.52 g, 0.01 mol) and II (0.91 g, 0.01 mol) was gently heated in an oil-bath, the temperature being raised gradually and kept at 160° for 3 hr. After cooling, the product was washed thoroughly with water and crystallised from water to give III, yield 1.0 g (49.26%), m.p. 167-68°; IR (KBr):3220 (NH), 1675 (C=O), 1600(C=N), 1150 cm^{-1} (C=S); PMR (DMSO-d_6): 7.28-7.95 (4H, *m*, Ar-*H*) (Found: C,53.0; H, 2.3; N,20.6; S,15.6. $C_9H_5N_3OS$ requires C,53.2; H,2.5; N,20.7; S,15.8%).

2-Amino-5,5a,6,9-tetrahydro-[1,3,4]*oxadiazolo*[2,3-*a*]*isoindol-5-one* (IV)

Finely powdered I (1.52 g, 0.01 mol) and II (0.91 g, 0.01 mol) were mixed thoroughly with freshly fused sodium acetate (1.64 g, 0.02 mol) and DMF (5 ml). The mixture was heated slowly in an oil-bath for 1 hr at 140° to get a clear solution and then at 160° for 2 hr with constant stirring, cooled to 100° and poured into ice water. The resulting brownish product was filtered, washed with water and crystallised from ethanol to get IV, yield 1.1 g (57.59%), m.p. 164-65°; IR (KBr): 3600-3340 (NH_2), 1740 cm^{-1} (C=O); PMR (DMSO-d_6) : 2.32 (2H,*m*,C_7-and C_8-H), 2.88 (2H,*s*,C_9-H_2), 3.65 (2H,*s*,C_6-H_2), 5.85 (1H,*t*,C_{5a}-H) (Found: C,56.4; H,4.6; N,21.8. $C_9H_9N_3O_2$ requires C,56.5; H,4.7; N,22.0%).

5(H)-Benzylidene-2(3H)-thioxo-[1,2,4]*triazolo*[5,1-*a*]*isoindole* (VI)

Finely powdered V (2.22 g, 0.01 mol) was mixed thoroughly with II (0.91 g, 0.01 mol) and the mixture gently heated in an oil-bath, the temperature being raised gradually till 120° when a clear solution was obtained. The mixture was further heated to 180° and kept at this temperature for 1 hr. After cooling, the product was washed thoroughly with water and crystallised from ethanol-water (50:50) to give VI as yellow needles, yield 1.9 g (68.59%), m.p. 165-66°; IR (KBr) : 3240 (NH), 170, (C=N), 1150 cm^{-1}, (C=S);PMR (DMSO-d_6) : 6.48 (1H, *s*, CH), 7.1-7.85 (9H,*m*,Ar-*H*) (Found : C,69.2; H,3.8; N,15.0; S,11.3. $C_{16}H_{11}N_3S$ requires C,69.3; H,4.0; N,15.2; S,11.6%).

3-(4-Methoxyphenyl)pentanedioic acid 5-thiosemicarbazide (VIII)

To a warm solution of VII (2.2 g, 0.01 mol) in dry benzene was added II (0.91 g, 0.01 mol) and the resultant mixture refluxed for 4 hr when a clear solution was obtained. On cooling, a white solid separat-

ed out, which was filtered, washed with little benzene and crystallised from acetone to give VIII as white needles, yield 2.9 g (93.25%), m.p. 165-66°; IR (KBr): 3400 (OH), 3300-3120 (NH, NH_2), 1700 (acid C=O), 1660 (amide C=O), 1180 cm^{-1} (C=S); PMR (DMSO-d_6): 2.33-2.66 (4H,*m*,CH_2), 3.41 (1H,*t*,C_3-H), 3.7 (3H,*s*,OCH_3), 6.83-7.17 (4H,*m*,Ar-*H*) (Found: C,49.9; H,5.5; N,13.4; S,10.2. $C_{13}H_{17}N_3O_4S$ requires C,50.2; H,5.5; N,13.5; S,10.3%).

4-(1,2-*Dihydro*-5-*thioxo*-1,2,4-*triazol*-3-*yl*)-3-(4-*methoxyphenyl*)*butanoic acid* (*IX*)

A solution of VIII (1 g) in sodium hydroxide (20 ml, 5%) was heated on a water-bath for 2 hr, cooled, acidified with dil-HCl and the precipitated solid filtered, washed with water and crystallised from acetone to get IX, yield 0.7 g (74.47%), m.p. 254-55°; IR (KBr): 3275 (OH), 3005 (NH), 1720 (acid C=O), 1600 (C=N); 1070 cm^{-1} (C=S); PMR (DMSO-d_6): 2.49-2.93 (4H,*m*,CH_2), 3.46 (1H,*t*,C_3-H), 3.7 (3H,*s*,OCH_3), 6.82-7.17 (4H,*m*,Ar-*H*), 13.17 (1H,*bs*,OH,D_2O exchangeable) (Found: C,53.1; H,5.0; N,14.1; S,10.8. $C_{13}H_{15}N_3O_3S$ requires C,53.2; H,5.1; N,14.3; S,10.9%).

7-(4-*Methoxyphenyl*)-[1,2,4]*triazolo*[1,5*a*]-*piperidin*-2(3*H*),5-*dione* (XI)

Compound IX (1 g) was refluxed with acetic anhydride (5 ml) for 3 hr, cooled and poured into ice water. The colourless solid, thus obtained, was filtered, washed with water and crystallised from acetic acid to get X, yield 0.8 g (74.07%), m.p. 170-71°; IR (KBr): 1720 and 1700 cm^{-1} (two C=O); PMR (DMSO-d_6): 2.47 (3H,*s*,CH_3), 3.05 (2H,*d*,C_8-H_2), 3.15 (1H,*s*,C_7-H), 3.35 (2H,*d*,C_6-H_2), 3.77 (3H,*s*,OCH_3), 6.82-7.24 (4H,*m*,Ar-*H*) (Found: C,56.7;H,4.5; N,13.1; S,10.0. $C_{15}H_{15}N_3O_3S$ requires C.56.8; H,4.7; N,13.2; S,10.1%).

7-(4-*Methoxyphenyl*)-[1,2,4]*triazolo*[1,5-*a*]piperidin-2(3H),5-dione (XI)

Compound VIII (1 g) on similar treatment with acetic anhydride as above gave XI, yield 0.6 g (72.29%), m.p. 180-81°, IR (KBr): 2910 (NH), 1720 and 1705 cm^{-1} (two C=O); PMR (DMSO-d_6): 2.2 (1H,*t*,C_7-H), 2.52 (2H,*d*,C_8-H_2), 3.0 (2H,*d*,C_6-H_2), 3.74 (3H,*s*,OCH_3), 6.9-7.32 (4H,*m*,Ar-*H*) (Found: C,60.0; H,4.9; N,16.1. $C_{13}H_{13}N_3O_3$ requires C,60.2; H,5.0; N,16.26).

1,2,5,6-*Tetrahydro*-5-(4-*chlorophenylhydrazone*)-4-(4-*methoxyphenyl*)-1-*thiourylpyridin*-2,6-*dione* (*XIII*)

A mixture of XII (3.57 g, 0.01 mol) and II (0.91 g, 0.01 mol) was refluxed with gl. acetic acid for 4 hr, cooled to 100° and poured into ice water when an orange coloured solid separated out. It was filtered, washed with water and chromatographed over silica gel using chloroform-ethyl acetate (2:1) as eluant to give XIII, yield 1.5 g (34.88%), m.p. 215-16°; IR (KBr): 3310-3200 (NH,NH_2), 1685 and 1640 (amide C=O), 1605 (C=N), 1250 cm^{-1} (C=S); PMR (DMSO-d_6): 3.8 (3H,*s*,OCH_3), 6.35 (1H,*s*,C_3-H), 7.05-7.7 (8H,*m*,Ar-*H*), 8.05 (2H,*bs*,NH_2), 9.75 (1H,*s*,NH), 14(1H,*s*,NH) (Found: C,52.8; H,3.6; N,16.1; S,7.3; Cl,8.3. $C_{19}H_{16}N_5O_3SCl$ requires C,53.0; H,3.7; N,16.3; S,7.4; Cl,8.4%).

5-*Methyl*-2(3*H*)*thioxo*-[1,2,4]*triazolo*[5,1-*a*]*isoquinoline*-6-*carboxylic acid* (XV)

Following the procedure as described for VIII, compound XIV (2.04 g, 0.01 mol) when treated with II (0.91 g, 0.01 mol) in dry benzene gave XV which crystallised from acetone, yield 1.3 g (50.19%), m.p. 169-70°; IR (KBr): 3200 (NH), 1740 (acid C=O), 1645 (C=N); 1180 cm^{-1} (C=S); PMR ($CDCl_3$): 1.96 (1H,*s*,NH,D_2O exchangeable), 2.6 (3H,*s*,CH_3), 7.5-8.36 (4H,*m*,Ar-*H*), 14.6 (1H,*s*,OH, D_2O exchangeable) (Found: C,55.5; H,3.4; N,16.0; S,12.1. $C_{12}H_9N_3O_2S$ requires C,55.6; H,3.5; N,16.2; S,12.4%).

References

1 Deshmukh N J, Kulkarni R A & Deodhar K D, *Indian J Chem*, **24B** (1985) 330.

2 Rao N R C, Venkataraghavan R & Kasturi T, *Can J Chem*, **42** (1964) 36.

3 Spinner E, *J chem Soc*, (1960) 1237.

4 Dziewonska M, *Spectrochim Acta*, **23A** (1967) 1195.

5 Becker H G O, Mell M J & Haufe H, *Wiss Z Tech Hochschule Leuna-Merschburg*, **8** (1966) 120; *Chem Abstr*, **64** (1966) 19596d.

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Structure of the 2-Isocyanatobenzoyl Chloride-Aluminium Chloride (1:2) Complex: Reactions with Some Nucleophiles

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The reactions of 2-isocyanatobenzoyl chloride-aluminium chloride (1:2) complex with methanol, aniline, methyl anthranilate, ethyl anthranilate, 2-aminobenzophenone, 2-amino-5-chlorobenzophenone have been studied. Based on the products obtained in these reactions, the 1:2-complex has been shown to be a mixture of acyclic and cyclic structures (**4**) and (**5**) respectively. This is in accordance with the observations recorded in IR studies.

Friedel-Crafts acylation of certain arenes[1] with 2-isocyanatobenzoyl chloride (**1**) affords 2-aminobenzophenones (**2**) at lower temperatures and 4,4-diaryl-1,4-dihydro-2*H*-3,1-benzoxazin-2-ones (**3**) at higher temperatures and/or with substrates of higher reactivity. The reaction proceeds through a common intermediate complex which was shown to exist exclusively in the cyclic structure 4-aryl-4-chloro-1,4-dihydro-2*H*-3,1-benzoxazin-2-one based on its reactions with different nucleophiles under both acidic and basic conditions[2]. Lewis acid complexes of acyl halides are also considered as intermediates in the Friedel-Crafts acylation reactions[3,4]. From an IR study of the aluminium chloride complexes of 2-isocyanatobenzoyl chloride, Misra *et al.*[5] have shown the complex formation to be complete with two mol equivalents of Lewis acid, and postulated that the 1:2-complex exists as an equilibrium mixture of acyclic and cyclic structures **4** and **5** respectively (Chart 1).

We have now carried out the reactions of the 2-isocyanatobenzoyl chloride-aluminium chloride (1:2) complex with methanol, aniline, methyl anthranilate, ethyl anthranilate, 2-aminobenzophenone and 2-amino-5-chloro-benzophenone and compared the reaction products with those obtained from **1** and the above nucleophiles with a view to establishing the structure of the **1**-$AlCl_3$ (1:2) complex.

Reaction with methanol

The reaction of **1** with two mol equivalents of methanol gave a mixture of N-carbomethoxyanthranilic acid (**6**), dimethyl isatoate (**7**) and isatoic anhydride (**8**). On the other hand, **1**-$AlCl_3$ (1:2) complex gave methyl anthranilate (**9**; 32%), N,N'-bis(2-carbomethoxyphenyl)urea (**10**; 8%), 3-(2-carboxyphenyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione (**11**; 7%), anthranilic acid (**12**; 18%) and a new compound identified as 3-methoxy-5-(2-carbomethoxyphenyl)-4*H*,6*H*-3,1,5-

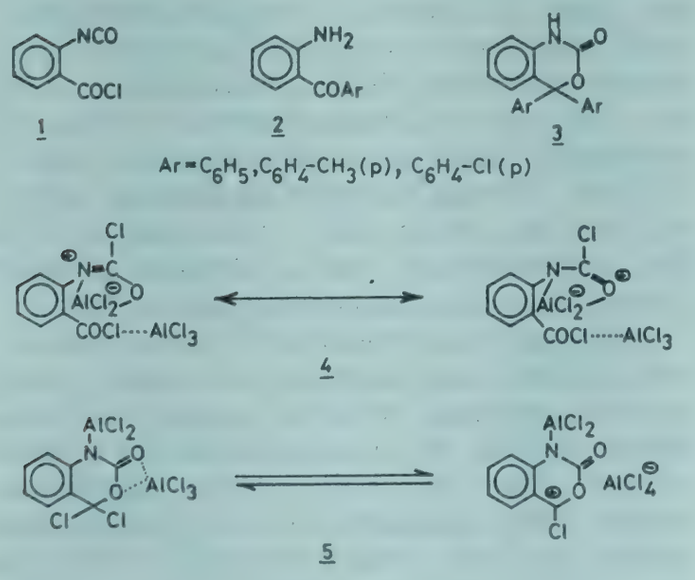
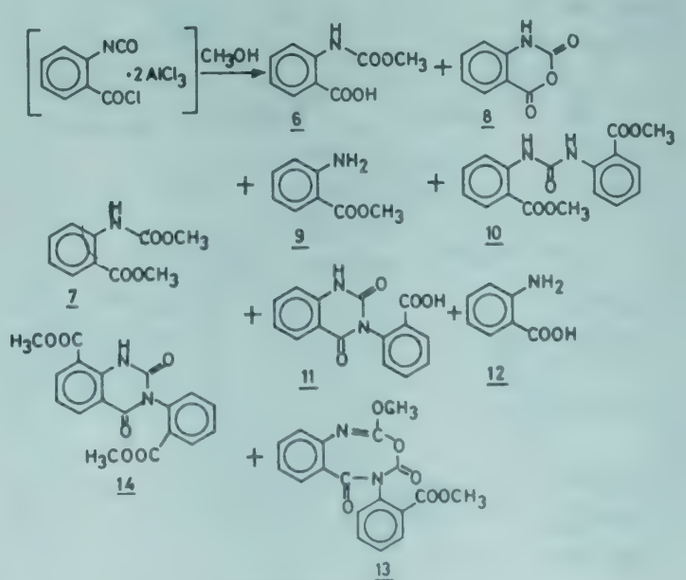


Chart 1



Scheme 1

benzoxadiazocine-4,6-dione (**13**, 3%) in addition to **6** (22%) and **8** (8%) (Scheme 1).

The new compound (m.p. 130°) showed characteristic IR absorptions at 1765, 1720 and 1680 cm^{-1} in the carbonyl region and no absorptions in the NH region. Its PMR($CDCl_3$) spectrum exhibited signals at δ 3.72 (*s*, 3H, OCH_3 at C-2), 3.97 (*s*, 3H, $COOCH_3$) and 7.2-8.7 (*m*, 8H, Ar−*H*). Its mass spectrum showed molecular ion peak at *m/z* 354 (44%) with significant ions at *m/z* 323, 310, 295, 279, 251, 236, 220, 146 (100%) and 90. The other possible structure **14** for the mass number 354 was outrightly rejected based on the number of aromatic protons and absence of NH signal in PMR spectrum as well as NH absorptions in IR spectrum. The mass spectrum was found to be very helpful for assigning its structure; the fragmentation pattern is shown in Chart 2. Other compounds were identified through their m.ps, m.m.ps and comparison of IR spectra with those of authentic samples[6].

Reactions with amines

2-Isocyanatobenzoyl chloride (**1**) reacted with one mol equivalent of aniline affording 3-phenyl-

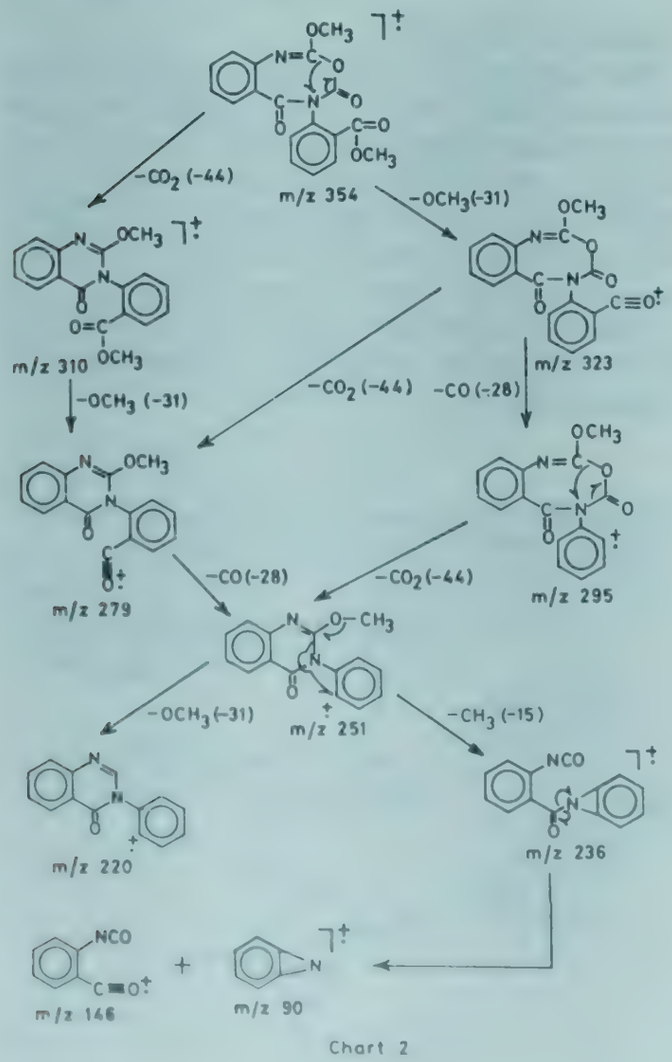
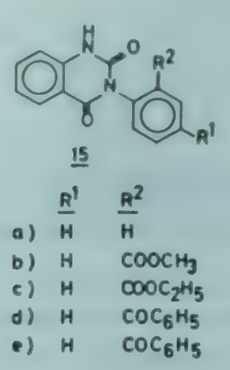


Chart 2



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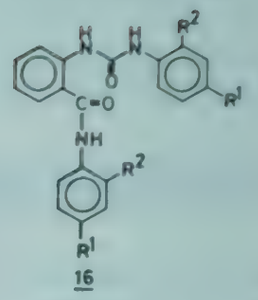
	R¹	R²
a)	H	H
b)	H	$COOCH_3$
c)	H	$COOC_2H_5$
d)	H	COC_6H_5
e)	H	COC_6H_5



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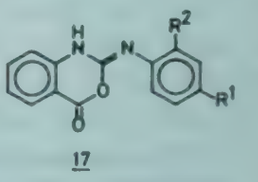

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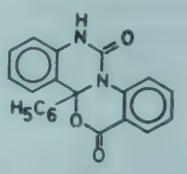

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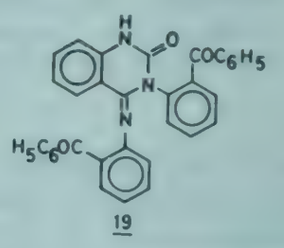


19

1,2,3,4-tetrahydroquinazoline-2,4-dione (**15a**), while with excess of aniline it produced *o*-phenylureidobenzanilide (**16a**)[7]. Analogously, methyl anthranilate, ethyl anthranilate, 2-aminobenzophenone and 2-amino-5-chloro-benzophenone reacted with **1** to afford[1,8] only the corresponding quinazolinediones (**15**).

The reaction of aromatic amines with **1**-$AlCl_3$ (1:2) complex furnished different types of products. One or two moles of aniline gave both **15a** and **16a**, while methyl or ethyl anthranilate afforded the ureidobenzanthranilide **16b** or **16c** as the major product. Besides, in the reaction with methyl anthranilate, 1,2-dihydro-2-(2-carbomethoxyphenylimino)-4*H*-3,1-benzoxazin-4-one (**17b**) was also obtained.

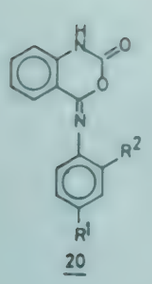
With 2-aminobenzophenone, the above complex gave 1,2-dihydro-2-(2-benzoylphenylimino)-4*H*-3,1-benzoxazin-4-one (**17d**), 11b-phenyl-7,11b-dihydroquinazolino[3,4-*a*][3,1]benzoxazine-6,13-dione (**18**) and 3-(2-benzoylphenyl)-4-(2-benzoylphenylimino)-1,2,3,4-tetrahydroquinazolin-2-one (**19**). But, 2-amino-5-chlorobenzophenone afforded only the corresponding benzoxazinone **17e**. The characterization data of different products obtained from these reactions are given in Table 1.

1,2-Dihydro-2-arylimino-4*H*-3,1-benzoxazin-4-ones (**17**) have been identified on the basis of their spectroscopic data, elemental analyses and their isomerisation to the quinazolindiones **15** in basic medium. Their IR spectra exhibited absorptions around 1765 assignable to C-4 carbonyl and around 1650 cm^{-1} due to exocyclic ν C=N. Ulrich *et al.*[9] observed the intensity of the C=N ab-

Table 1—Products Distribution in the Reaction of Amines with **1**-$AlCl_3$ (1:2) Complex (0.01 mol) and Their Characterisation Data*

Reactant (g, mol)	Products	m.p. °C	Yield (%)	IR: (nujol) (cm^{-1})	PMR($CDCl_3$) (ppm)	MS (*m/z*)
Aniline (0.93, 0.01)	**15a**	272 (247)[7]	41	3275 (N – H), 1710 amido, C = O), 1645 (ureido, C = O)..	—	—
	16a	217 (211)[7]	23	3300, 3205 (N – H), 1695 (amido, C = O), 1635 (ureido, C = O).	—	331 (M^+, 5.3%), 239 (23), 238 (50), 212 (35), 146 (57), 121 (11), 120 (100), 119 (76), 93 (88), 92 (74), 91 (39), 90 (26).
	8	252	19	3250, 3175, 3105 (N – H), 1760 (C – 4, C = O), 1715 (C – 2, C = O).	—	—
(1.86, 0.02)	**15a**		15			
	16a		77			
	8		6			
Methyl anthranilate (3.02, 0.02)	**16b**	248	52	3250 (N – H), 1720 (ester, C = O), 1685 (amido, C = O), 1650 (ureido, C = O)	3.9 (*s*, 6H, 2 × OCH_3), 6.8-8.5 (*m*, 12H, Ar – *H*), 15.6(*s*, 1H,NH), 15.9 (*s*, 1H, NH), 16.9 (*s*, 1H, NH).	447 (M^+, 1%), 415 (2), 296 (12), 270 (11), 265 (8), 237 (40), 177 (9), 151 (44), 146 (100), 128 (80), 119 (48), 92 (44), 91 (52).
	17b	126	17	3250 (N – H), 1765 (C – 4, C = O), 1680 (ester, C = O), 1650 (exocyclic, C = N), 1010 (C – O – C).	3.95 (*s*, 3H, OCH_3), 7.0-8.9 (*m*, 8H, Ar – *H*). 10.97 (*s*, 1H, NH)	296 (M^+, 46%), 264 (17), 237 (50), 146 (100), 119 (10), 118 (9), 92 (9).
Ethyl anthranilate (3.3, 0.02)	**16c**	135	61	3235 (N – H), 1705 (ester, C = O), 1670 (amide, C = O), 1650 (ureido, C = O).	1.49 (*t*, 6H, 2 × CH_3), 4.41 (*q*, 4H, 2 × OCH_2), 7.0-8.66 (*m*, 12H, Ar – *H*), 10.69 (*s*, 1H, NH), 10.96 (*s*, 1H, NH), 12.9 (*s*, 1H, NH)	475 (M^+, 2%), 429 (2), 310 (16), 284 (13), 265 (32), 237 (27), 191 (3), 165 (98), 146 (100), 120 (52), 119 (51), 92 (41), 91 (11).
	8		28			
2-Aminobenzophenone (1.97, 0.01)	**17d**	171	6	3100 (N – H), 1740 (C – 4, (C – 4, C = O), 1625 (ArCOAr), 1620 (exocyclic, C = N), 1025 (C – O – C).	6.72-8.15 (*m*, 13H, Ar – *H*), 11.6 (*s*, 1H, NH).	342 (M^+, 7.5%), 265 (4), 237 (27), 146 (100), 119 (8), 105 (10), 92 (7), 91 (8), 90 (88).
	18	294	22	3250 (N – H), 1725 (C – 5, C = O), 1685 (C – 12, C = O).	6.7-8.02 (*m*, 13H, Ar – *H*), 10.65 (*s*, 1H, NH).	342 (M^+, 16%), 298 (50), 297 (100), 265 (25), 264 (98), 146 (98), 118 (8), 90 (48), 77 (35)
	19	316	30	3200 (N – H), 1670 (C = O), 1660 (C = N), 1640 (ArCOAr).	6.18-7.96 (*m*, 22H, Ar – *H*), 9.27 (*s*, 1H, NH).	521 (M^+, 70.0%), 492 (15), 444 (27), 416 (100), 326 (12), 325 (38), 297 (76).
2-Amino-5-chloro-benzophenone (2.31, 0.01)	**17e**	222	50	3235 (N – H), 1775 (C – 4, C = O), 1635 (ArCOAr), 1625 (exocyclic, C = N), 1015 (C – C – O).	7.34-8.91 (*m*, 12H, Ar – *H*) 10.56 (*s*,1H, NH).	376 (M^+, 6.0%), 299 (1), 271 (14), 146 (100), 105 (9), 92 (4), 91 (6), 90 (75), 77 (28).
	8		25			

*Satisfactory C, H and N analyses were obtained for all the compounds.



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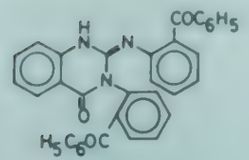

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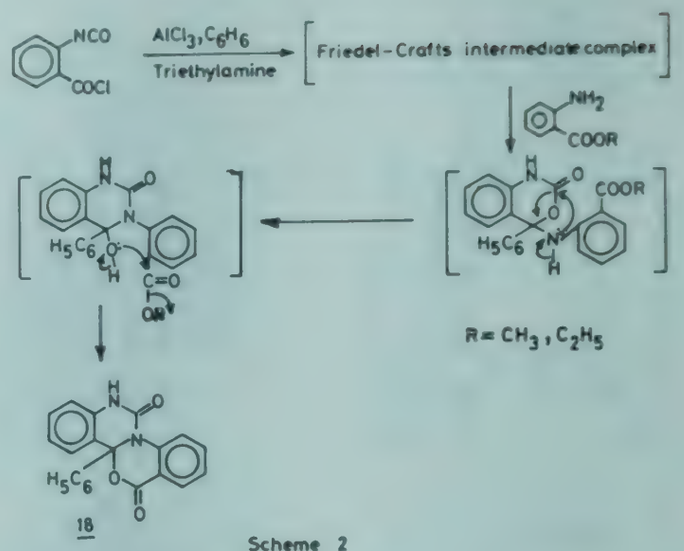
sorption to be weaker than that of C=O in the case of endocyclic C=N in 3,1-benzoxazin-4-ones whereas in the present case, the absorptions for C=N were found to be as strong as those of νC=O. The other isomeric structure **20** was eliminiated since no peak due to loss of CO_2 (44 mass unit) from the molecular ion was observed in the mass spectrum.

Similarly, the compound **19** was identified as 3-(2-benzoylphenyl)-4-(2-benzoylphenylimino)-1,2,3,4-tetrahydroquinazolin-2-one mainly on the basis of its conversion into the known quinazolinedione (**15d**) and 2-aminobenzophenone (**2**, Ar = C_6H_5) by acid hydrolysis and by the absence of IR absorption around 1720 cm^{-1} assignable to C-4 carbonyl in the isomeric quinazolin-4-one[1,6] (**21**).

The compound **18** (mass number 342) showed IR bands at 3250, 1725 and 1680 cm^{-1}. Its PMR($CDCl_3$) spectrum exhibited signals at δ 6.7-8.07 (*m*, 13H, Ar−*H*) and 10.65 (*s*, 1H, NH). Besides $M^{+\cdot}$, other prominent ions in its mass spectrum were observed at *m/z* 298, 297, 265, 264, etc. Out of the four isomeric structures, **15d**, **17d**, **20d** and **18**, the first three were eliminated based on appearance of only two absorptions in the carbonyl region in the IR spectrum and the absence of peaks at *m/z* ($M^+ - 105$) and 105 in the mass spectrum due to loss of free $-COC_6H_5$ moiety. The two absorptions at 1725 and 1685 cm^{-1} were assignable to C5 and C-12 carbonyls, respectively for the structure **18**. Thus, the compound was identified as 11b-phenyl-7,11b-dihydroquinazolino[3,4-*a*]benzoxazine-6,13-dione. This compound was obtained earlier[2] by the action of methyl or ethyl anthranilate in the basic medium on the intermediate complex obtained with **1** (Scheme 2) and has been found identical with the one obtained now in m.p., m.m.p. and superimposable IR spectrum.

From the foregoing account, it is seen that 2-isocyanatobenzoyl chloride reacts with methanol and gives products formed by preferential attack at the linear isocyanato function. However, formation of methyl anthranilate (**9**) and N,N′-bis(2-carbomethoxyphenyl)urea (**10**) as major products from **1**-$AlCl_3$ (1:2) complex can be ex-



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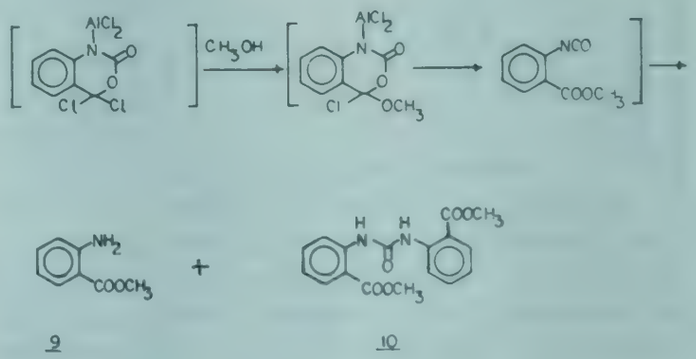
Scheme 2



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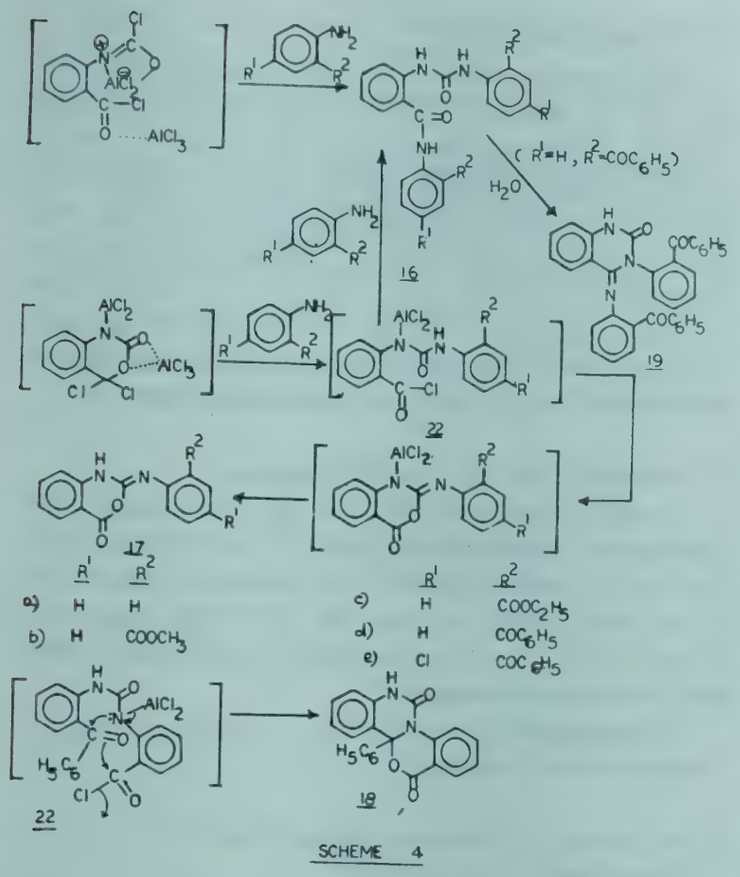
SCHEME 3

plained only from the cyclic structure **5** (Scheme 3); other compounds isolated can arise from the acyclic structure **4** of the complex.

In the reactions with aniline and *ortho*-substituted anilines (amines added to the reagent), the parent compound afforded 3-substituted-1,2,3,4-tetrahydroquinazolin-2,4-diones (**15**) as the major products. On the other hand, **1**-$AlCl_3$ (1:2) complex gave ureidobenzanilides (**16**) as major products when reacted with aniline and alkyl anthranilates. These can arise either from the cyclic or acyclic structure. In view of the higher nucleophilicity of amines relative to methanol, ring opening by attack at C-2 carbonyl of the cyclic complex **5** predominates. The intermediate *o*-ureidobenzoylchloride (**22**) can react with a second molecule of amine affording **16**.

Alternatively, **22** undergoes recyclisation via oxygen forming 1,2-dihydro-2-arylimino-4*H*-3,1-benzoxazin-4-one (**17**); cyclisation via ureido nitrogen of the ureido benzanilide (**16d**) followed by loss of water gives the iminoquinazolinone **19**. The formation of **18** in the reaction with 2-aminobenzophenone can also arise from the same in-



SCHEME 4

termediate **22d**. The overall reaction is depicted in Scheme 4.

Bhatt and co-workers[10] have examined several keto acid chloride and dicarbonyl dichloride systems for the existence of ring-chain tautomerism through kinetic and spectroscopic studies. They opine that no tautomerism exists and the γ-keto acid chlorides exist exclusively in the cyclic or acyclic form. They have further shown that in the case of some δ-keto acid chlorides and 1,2- and 1,3-dicarbonyl dichlorides, both the forms co-exist; however, no evidence for any equilibrium between the two forms could be adduced.

In the present case of **1**-$AlCl_3$ (1:2) complex, all the chemical reactions clearly show it to be a mixture of cyclic and acyclic structures in agreement with its IR data[5]. However, the existence or absence of any equilibrium between the two structures cannot be postulated with certainty.

Experimental Procedure

Melting points were recorded on a Buchi melting point apparatus and are not corrected. Yields given are those obtained after crystallization. IR spectra (ν_{max} in cm^{-1}) in nujol were recorded on a Perkin-Elmer 337 spectrometer, PMR spectra (chemical shifts expressed in δ, ppm) in $CDCl_3$ and DMSO-d_6 on a Varian EM-390 and JEOL-FX-FT 100 MHz instruments using TMS as internal standard, and mass spectra on AEI-MS-3074 and Hewlett Packard GC/MS 5995 spectrometers. Microanalyses were carried out on a Sargent Micro-combustion apparatus.

2-Isocyanatobenzoyl chloride was (**1**) prepared from isatoic anhydride following the procedure of Iwakura *et al.*[7] and was redistilled before use. Reagent grade aluminium chloride sublimed *in vacuo* at 60 mm Hg pressure in an apparatus similar to the one used by Cook[11] was powdered and used as such. Ethylene chloride was purified by treating with anhyd. aluminium chloride following the procedure of Misra[6].

Preparation of **1**-$AlCl_3$ (1:2) *complex*

2-Isocyanatobenzoyl chloride (**1**; 1.81 g, 0.01 mol) in ethylene chloride (20 ml) was added to a suspension of aluminium chloride (2.62 g, 0.02 mol) in ethylene chloride (20 ml) and the mixture stirred for 1 hr. The resulting greenich brown solution was subjected to different reactions:

Reaction with methanol

The **1**-$AlCl_3$ (1:2) complex, prepared above, was added slowly with stirring to methanol (15 ml) in ethylene chloride (15 ml) when the temperature rose to 55°. The reaction mixture was further stirred for 45 min, and decomposed with ice-cold water. The solid that separated out was identified as 3-(2-carboxyphenyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione (**11**; 0.1 g, 7%), m.p. 206° (methanol) (lit.[12], m.p. 298-300°); IR: 3150 (N−H), 2640, 2450 (COOH), 1730 (amide C=O), 1680 (acid C=O), 1665 (ureido C=O); PMR($CDCl_3$ − DMSO-d_6): 7.05 (*s*, 1H, COOH), 7.25-7.7 (*m*, 8H, Ar−*H*), 10.9 (*s*, 1H, NH); MS: *m/z* 282 (M^+, 60%), 264 (9), 237 (100), 146 (70), 119 (75).

From the filtrate, the organic layer was separated and aq. layer extracted with benzene (2×50 ml). From the combined organic layer, the solvent was removed *in vacuo* and the residue subjected to column chromatography when the following compounds were isolated.

The benzene-hexane (3:1) fraction gave methyl anthranilate (**9**; 0.5 g, 32%), and N,N'-bis(2-carbomethoxyphenyl)urea (**10**; 0.13 g, 8%), m.p. 145° (benzene-hexane) (lit.[11] 144°); IR: 3250 (N−H), 1680 (ester C=O), 1660 (ureido C=O); PMR($CDCl_3$): 3.95 (*s*, 6H, 2×OCH_3), 7.5-8.5 (*m*, 8H, Ar−*H*), 10.8 (br *s*, 2H, 2NH); MS: *m/z* 328 (M^+, 84%), 297 (2), 265 (8), 237 (3), 177 (8), 151 (96), 146 (67), 119 (100).

Elution with benzene gave 3-methoxy-5-(2-carbomethoxyphenyl)-4*H*,6*H*-3,1,5-benzoxadiazocine-4,6-dione (**13**; 0.05 g, 3%), m.p. 130° (benzene-hexane); IR: 1765 (C-4,

C=O), 1720 (C-6, C=O), 1680 (ester C=O); PMR($CDCl_3$): 3.72 (*s*, 3H, OCH_3 at C-2), 3.97 (*s*, 3H, $COOCH_3$), 7.2-8.7 (*m*, 8H, Ar−*H*); MS: *m/z* 354 (M^+, 44%), 323 (3), 310 (4), 295 (25), 279 (25), 251 (55), 236 (7), 220 (37), 146 (100), 90 (36).

The benzene-ethyl acetate (19:1) eluate gave N-carbomethoxyanthranilic acid (**6**; 0.43, 22%), m.p. 176° (lit.[12,13] 181°); IR: 3340 (N−H), 1750 (carbamate C=O), 1660 (acid C=O); PMR($CDCl_3$): 2.56 (*s*, 1H, COOH); 3.79 (*s*, 3H, OCH_3), 7.03-8.49 (*m*, 4H, Ar−*H*), 10.93 (*s*, 1H, N*H*); MS: *m/z* 197 (M^+, 1.09%), 196 (7.29), 195 (67.52), 177 (19.79), 146 (96.02), 147 (10), 120 (11.9), 119 (67.35), 92 (70.32), 91 (20.84), 15 (100).

The compound isolated by elution with benzene-ethyl acetate (9:1) was identified as isatoic anhydride (**8**; 0.15 g, 8%).

The aqueous layer showed a single spot on TLC. It was extracted into ethyl acetate (4×25 ml), the extract dried ($MgSO_4$), solvent remvoed *in vacuo* and the residue on trituration with benzene-hexane (1:1) yielded anthranilic acid (**12**; 0.25 g, 19%), m.p. 143°, identified through m.m.p. and superimposable IR spectrum with an authentic sample.

Reactions with amines

To the prepared **1**-$AlCl_3$ (1:2) complex was added the desired amine in ethylene chloride (20 ml) during 10 min and the reaction mixture stirred further for 3 hr, poured into ice-cold water (100 ml) and extracted with benzene (2×50 ml). The extract was dried ($MgSO_4$), solvent removed *in vacuo* and the residue chromatographed over silica gel column eluting successively with benzene-hexane (1:1), benzene and benzene-ethyl acetate (19:1 and 9:1). The compounds thus obtained were recrystallised from methanol. Their characterisation data are given in Table 1.

Conversion of benzoxazinones **17** *into quinazolinediones* (**15**)

(*a*) *Conversion of* **17b**

1,2-Dihydro-2-(2-carbomethoxyphenyl imino)-4*H*-3,1-benzoxazin-4-one (**17b**) (250 mg) was refluxed in 5% acetonic KOH solution (20 ml) overnight, solvent removed and the residue treated with a few drops of methanol to give 3-(2-carbomethoxyphenyl)-1,2,3,4-tetrahydroquinazoline-2,4-dione (**15b**) (210 mg, 81%), m.p. 256° (methanol), IR: 3200 (N−H), 1725 (ester, C=O), 1675 (amido, C=O), 1655 (ureido, C=O). The IR data were identifical with those of an authentic sample[8].

(*b*) *Conversion of* **17e**

Analogously, **17e** (150 mg) afforded **15e** (95 mg, 64%), m.p. 254° (methanol); IR: 3200, 3140 (N−H), 1715 (amide, C=O), 1660 (Keto C=O), 1650 (ureido C=O); PMR($CDCl_3$−DMSO-d_6): 6.9-7.85 (*m*, 12H, Ar−*H*), 11.37 (*s*, 1H, NH); MS: *m/z* 376 (M^+, 3%), 299 (3), 271 (100), 146 (20) (Found: C, 67.0; H, 3.5; N, 7.4. Calc. for $C_{21}H_{13}ClN_2O_2$: C, 77.0, H, 3.5; N, 7.5). Its identity was confirmed by m.m.p. determination and superimposable IR spectrum with an authentic sample[8].

Hydrolysis of **19** *with hydrochloric acid*

To the compound **19** (520 mg) was added 20% methanolic hydrochloric acid (2 ml of conc. HCl in 8 ml of methanol) and the mixture refluxed for 4 hr, and cooled to give **15d** (300 mg), m.p. and m.m.p. 252°; its IR spectrum was identical with that of authentic sample[1].

2-Aminobenzophenone (**2**; 190 mg) was recovered from the filtrate.

11*b*-*Phenyl*-7,11*b*-*dihydroquinazolino*[3,4-*a*][3,1]-*benzoxazine*-6,13-*dione* (**18**)[2]

To a stirred suspension of aluminium chloride (3.93 g, 0.03 mol) in benzene (30 ml) was added **1** (1.81 g, 0.01 mol) in benzene (20 ml) during 10 min while maintaining the temperature at 25±2°C. After stirring further for 45 min at the same temperature, the reaction mixture was cooled to 10° and triethylamine (5.05 g, 0.05 mol) in benzene (30 ml) added to it during 15 min. After 10 min methyl anthranilate (1.51 g, 0.01 mol) in benzene (20 ml) was added to it during 15 min at the same temperature and the reaction mixture stirred further for 3 hr at room temperature. Usual work-up and column chromatography over silica gel using benzene-ethyl acetate (17.3) as eluant afforded **18** (1.8 g, 53.2%). Crystallisation from methanol gave analytical sample.

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References

1 Misra B K, Rao Y R & Mahapatra S N, *Indian J Chem*, **22B** (1983) 1132.

2 Acharya B P & Rao Y R, *J chem Res* (*S*), (Communicated).

3 Gore P H, *Chem Rev*, **55** (1965) 229.

4 Olah G A, *Fridel-Crafts and related reactions*, Vol. I (Wiley Interscience, New York) 1963, 623.

5 Misra B K, Rao Y R & Mahapatra S N, *J chem Soc Perk Trans*-2, (1983) 897.

6 Misra B K, *Synthetic studies on polycyclic compounds—Certain N-heterocycles from 2-isocyanatobenzoyl chloride*, Ph D Thesis, Utkal University, 1981.

7 Iwakura Y, Uno H & Kang S, *J org Chem*, **31** (1966) 142.

8 Our unreported results.

9 Ulrich H, Tucker B & Sayigh A A R, *J org Chem*, **32** (1960) 4052.

10 Bhatt M V, Ei Ashry S H & Somayaji V, *Indian J Chem*, **19B** (1980), 473 and references cited therein.

11 Cook D, *Can J Chem*, **37** (1959) 48.

12 Peet N P, Sunder S & Brown W H, *J org Chem*, **41** (1976) 2728.

13 Doleschall G & Lempert K, *Mh Chem*, **95** (1964) 1083.

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Thermal Claisen Rearrangement of Bisprenyl Ether of 4,6-Diacetylresorcinol

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The thermal Claisen rearrangement of the bisprenyl ether (**2**) of 4,6-diacetylresorcinol (**1**) has been studied by refluxing in different solvents like N,N-dimethylaniline, *o*-xylene and *n*-decane and also by heating it neat in a sealed tube at 155° and 185°. 5,7-Diacetyl-2,3-dihydro-4-hydroxy-2,3,3-trimethylbenzofuran (**3**) is found to be the major product along with 3-acetyl-2,4-dihydroxy-5-(3,3-dimethylallyl)acetophenone (**4**) and 5-acetyl-2,4-dihydroxy-3-(3,3-dimethylallyl)acetophenone (**5**). The products have been characterised by their spectral data (IR, UV, PMR and mass) and their formation has been rationalised.

Thermal Claisen rearrangements[1,2] of the bisallyl ethers of 4,6- and 2,4-diacetylresorcinols[3,4] were carried out in our laboratory and formation of a variety of products arising by the loss of an acetyl group, [1,5] sigmatropic H and acetyl shifts etc., was noticed. A few of the rearranged products were considered to be useful synthons for preparing some natural α-, and γ-benzopyrones. Similar rearrangement studies on aryl prenyl ethers assume greater significance and are expected to yield rearranged products of more synthetic value as a yield rearranged products of more synthetic value as a large number of the natural compounds have O-prenyl, C-prenyl or dimethylpyran or substituted furan components[5]. With this objective in view, we have now studied thermal Claisen rearrangement of the diprenyl ether (**2**) of 4,6-diacetylresorcinol (**1**) in solvents like N,N-dimethylaniline, *o*-xylene and *n*-decane. The rearrangement was also studied by heating the compound in a sealed tube at 155° and 185°.

The bisprenyl ether (**2**), prepared now from **1** and characterised, was refluxed in N,N-dimethylaniline (b.p. 193°) for 3 hr. Careful work-up followed by preparative TLC led to the isolation of 5,7-diacetyl-2,3-dihydro-4-hydroxy-2,3,3-trimethylbenzofuran (**3**, 30%) and 3-acetyl-2,4-dihydroxy-3-(3,3-dimethyllyl)acetophenone (**4**, 6%). These were fully characterised by elemental analyses and spectral data (see Experimental). In view of the poor yields and significant resinification the rearrangement was studied in low boiling *n*-decane (b.p. 171-75°) and *o*-xylene (b.p. 144°). In both the solvents, in addition to **3** and **4**, 5-acetyl-2,4-dihydroxy-3-(3,3-dimethyllyl) acetophenone (**5**, 8-11%) was also isolated and charactgerised. Thermal rearrangement of **2** carried out in a sealed tube at the boiling point (b.p. 185°) of aniline gave **3** (9%) and **4** (2%) while rearrangement at boiling temperature (b.p. 155°) of anisole yielded **5** in addition to **3** and **4**.

The formation of **3** may be explained by the *ortho* rearrangement of one of the prenyl groups with concomitant cyclisation and deprenylation of the other prenyl group. But, the formation of **4** must involve a multiple rearrangement (Chart 1) including a [1,5] sigmatropic acetyl shift, as observed earlier[1,2] in the rearrangement of the bisallyl ether (**6**), and an elimination of a prenyl group after *para* rearrangement of the intermediate (D). The loss of 1,1-dimethylpropene-2 in preference to 3,3-dimethylpropene-2 is understandable in view of greater relief from the steric interaction[6] in the dienone. Product **5** should have been formed by C-prenylation, probably, by the liberated prenyl cation. If it were so, C-prenylation would be expected to give rise to **7** as a major product by a more stable prenyl cation. The formation of **7**, expected normally through *o*-Claisen migration of **2**, can not be ruled out by this process as well. In any case it undergoes concomitant cyclisation to **3**. In fact **5** is obtained only as a minor product in the reaction.

It is interesting to note that no product arising by the loss of an acetyl group has been noticed unlike in the rearrangement of the bisallyl ether (**6**). It might be that a prenyl group is preferentially lost as compared to an acetyl group while the loss of an allyl or acetyl group is competitive. The difference in prenyl and allyl ethers is obvious when we look at the intermediate dienone structure (A) where a rearranged prenyl group exerts more steric influence compared to that of an allyl group.

The trimethylbenzofuran (**3**) appears a useful syn-

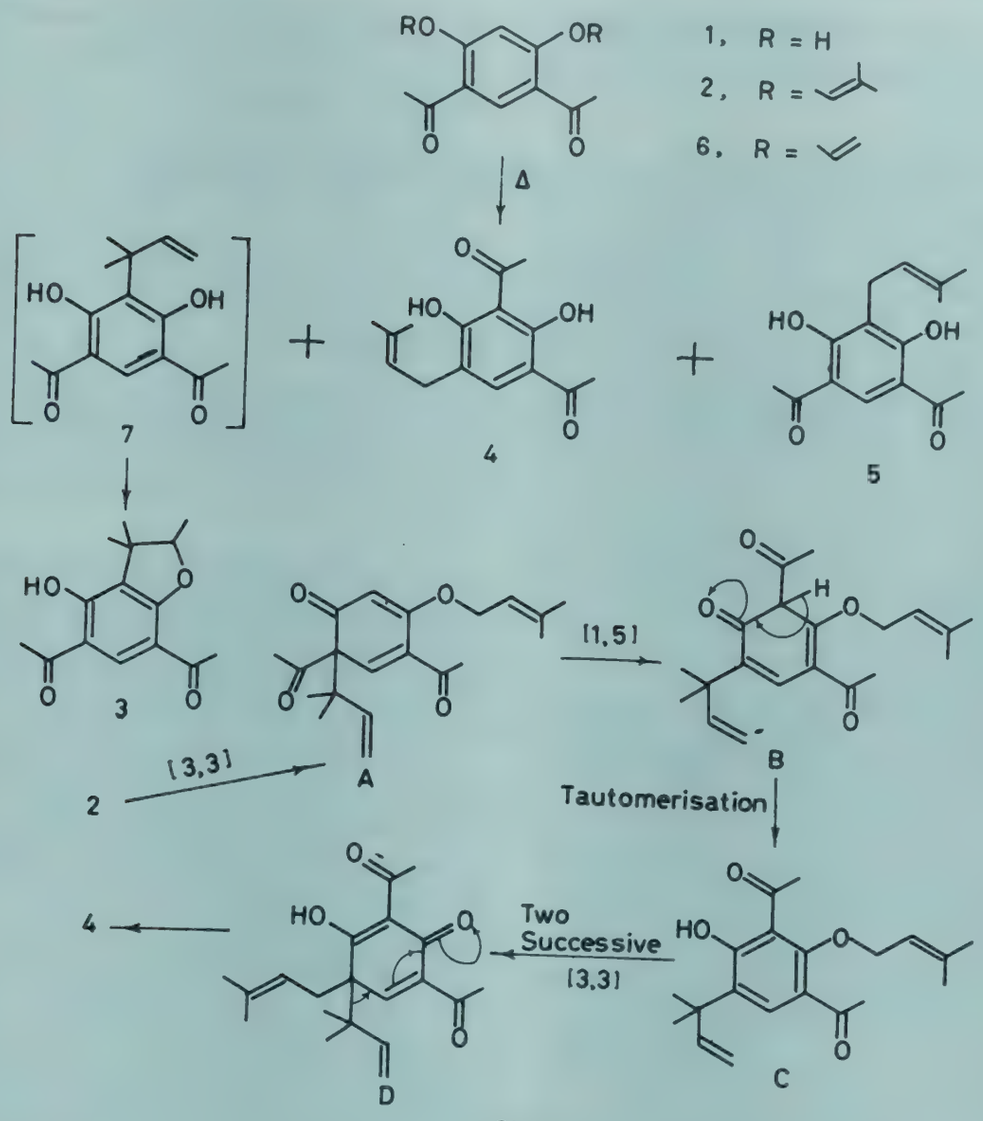

Chart 1

thon to prepare some analogues of natural compounds by building up an additional γ-pyrone unit as in neishoutin[5].

Experimental Procedure

All the melting points, determined on electrical hot plate, are uncorrected. Unless otherwise stated, IR spectra (ν_{max} in cm^{-1}) were recorded in $CHCl_3$ on a Shimadzu-IR-408 spectrophotometer, PMR spectra in $CDCl_3$ on a Perkin-Elmer R 32 (90 MHz) spectrometer (chemical shifts in δ-scale downfield from TMS), UV spectra in EtOH on a Shimadzu-UV-260 and mass spectra on Hitachi RMU-6E. Preparative TLC was performed using silica gel-G (Acme) and column cromatography using silica gel (100-200 mesh, Acme).

5-Acetyl-2,4-bis(3,3-dimethylallyoxy)acetophenone (**2**)

A mixture of **1** (1 g, 0.005 mol), 3,3-dimethylallyl bromide (0.6 ml, 0.0103 mol) and freshly ignited K_2CO_3 (5 g) was refluxed in dry acetone (50 ml) for 3 hr. The acetone solution was distilled under reduced pressure and the resulting product was treated with water and extracted with $CHCl_3$ (3 × 50 ml). The combined chloroform extract was dried ($MgSO^4$), evoparated, and the pale yellow solid obtained crystallised from *n*-hexane-$CHCl_3$ to afford **2** as colourless shining needles (1.64 g, 99%), m.p. 103-4° (Found: C, 74.8; H, 8.2. $C_{20}H_{26}O_4$ requires C, 75.0; H, 8.1%); IR (KBr): 1675 (>C=O), 1590, 1355, 1280 and 1230 cm^{-1}; UV: 210, 250, 280 and 310 nm; PMR: 2.46 (*s*, 6H, 2 × $-COCH_3$), 4.62 (*d*, 4H, J = 7.87, 2 × $-OCH_2-$), 5.45 (*t*, 2H, J = 6.75 Hz, 2 × $-CH_2-CH=$), 1.8 (*s*, 12H, 2 × *gem* CH_3), 6.36 (*s*, 1H, C_3-H) and 8.2 (*s*, 1H, C_6-H).

Thermal rearrangement of **2**: *(a) In, N,N-dimethylaniline*

2 (1 g, 0.003 mol) was refluxed in freshly distilled N,N-dimethylaniline (10 ml) for 3 hr. The reaction mixture was poured into ice cold HCl (300 ml) and the resulting dark reddish brown oil extracted with $CHCl_3$ (3 × 100 ml). The combined chloroform extract was washed with water (3 × 100 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy product (800 mg). It showed three spots on TLC; R_f: 0.44, 0.68 and 0.92 (C_6H_6 -

EtOAc, 9:1). Preparative TLC of the above product mixture yielded compounds **3** and **4** besides starting **2** (30 mg, 3%) (R_f: 0.44).

5,7-Diacetyl-2,3-dihydro-2,3,3-trimethylbenzofuran (**3**)

It crystallised as colourless needles from pet ether (300 mg, 30%), m.p. 71-72°. It gave reddish brown colour with alc. $FeCl_3$ (Found: C, 68.5; H, 6.9. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); IR: 2950, 1670 (>C=O), 1635 (chelated >C=O), 1590, 1450, 1365 and 1320; UV: 200 (1.819), 240 (1.148), 260 (2.648) and 320 (1.194); PMR: 2.49 (*s*, 6H, *gem* CH_3), 4.55 (*q*, 1H, J = 7.87 Hz, C_2-H), 8.3 (*s*, 1H, C_6-H), 12.88 (*s*, 1H, C_4-OH); (*m/z*, relative intensity) : 262 (M^+, 5.43%), 261 (35%), 247 (12.6%), 246 (64.3%), 228 (17.7%), 204 (29.7%), 190 (10.8%), 69 (19.5%) and 43 (100%).

3-Acetyl-2,4-dihydroxy-5-(3,3-dimethylallyl)acetophenone (**4**)

It came out as colourless needles from pet ether (R_f: 0.72) (60 mg, 6%), m.p. 65-66°. It gave red colour with alc. $FeCl_3$ (Found: C, 68.7; H, 6.9, $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); IR: 1710 (>C=O), 1635-1550 (chelated >C=O), 1450, 1380, 1375, 1325, 1080 and 970; UV: 210 (2.913), 270 (2.674) and 350 (1.493); PMR: 1.7 (*s*, 3H, C_3-CH_3), 1.75 (*s*, 3H, C_3-CH_3), 2.54 (*s*, 3H, C_3-$COCH_3$), 2.75 (*s*, 3H, C_1-$COCH_3$), 3.25 (*d*, 2H, J = 9 Hz, C_5-CH_2-), 5.25 (*t*, 1H, J = 7.87 Hz, C_5-CH_2-C*H*=), 14.7 (*s*, 2H, 2× −OH); MS (*m/s*, rel. int.): 262 (M^+, 13.3%), 261 (77.5%), 246 (28.6%), 232 (65.2%), 228 (20.7%), 291 (69.1%), 218 (54.7%), 207 (68.1%), 206 (61.3%), 204 (10.2%), 200 (16.5%), 191 (23.9%), 189 (15.2%), 148 (44.6%), 91 (7.6%), 77 (10.9%), 69 (7.6%) and 43 (100%).

(b) *In n-decane*

2 (1 g, 0.003 mol) was refluxed in *n*-decane (10 ml) for 18 hr. The reaction mixture was worked-up by passing it over a column of silica gel (50 g). The initial *n*-hexane fractions removed *n*-decane (10 ml). Further elution did not yield any pure component but a mixture of four compounds; R_f 0.36, 0.66, 0.70 and 0.90 (C_6H_6 - EtOAc, 9.5:0.5). This mixture on preparative TLC yielded a new acetophenone derivative **5**, in addition to **1** (15 mg, 1.5%), **3** (60 mg, 6%) and **4** (60 mg, 6%).

5-Acetyl-2,4-dihydroxy-3-(3,3-dimethylallyl)acetophenone (**5**)

It crystallised as colourless needles from pet ether (R_f: 0.90) (80 mg, 8%), m.p. 89-90°. It gave brown colour with alc. $FeCl_3$ (Found: C, 68.6; H, 6.9. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); IR: 1640 (>C=O), 1620, 1450, 1355, 1325, 1125, 1070 and 905; UV: 200 (1.714), 260 (2.173) and 320 (1.428); PMR: 1.65 (*s*, 3H, C_3-CH_3), 1.76 (*s*, 3H, C_3-CH_3), 2.5 (*s*, 6H, 2× $-COCH_3$), 3.5 (*d*, 2H, J = 9 Hz, C_3-CH_2-), 5.2 (*t*, 1H, J=9 Hz, C_3-CH_2-C*H*=), 8.1 (*s*, 1H, C_6-H), 13.22 (*s*, 2H, 2× −OH); MS (*m/z*, rel. int.): 262 (M^+, 7.8%), 261 (48.1%), 247 (9%), 246 (46.7%), 232 (6.3%), 228 (7.1%), 220 (4.7%), 218 (10.7%), 207 (3.9%), 206 (33.9%), 205 (2.37%), 204 (14.2%), 202 (3.73%), 200 (1.82%), 191 (13%), 186 (8.7%), 77 (6.5%), 69 (5.43%) and 43 (100%).

(c) *In xylene*

2 (1 g, 0.003 mol) was refluxed in freshly distilled *o*-xylene (10 ml) for 90 hr. The pale yellow reaction mixture yielded **1** (20 mg, 2%), **2** (100 mg, 10%), **3** (90 mg, 9%), **4** (100 mg, 10%) and **5** (110 mg, 11%).

(d) *Heating at* 150° *in a sealed tube*

2 (1 g, 0.003 mol) was heated in a sealed tube at 150° for 8 hr. The resulting reddish reaction mixture on preparative TLC using benzene as developing solvent yielded **1** (40 mg, 4%), **3** (200 mg, 20%), **4** (60 mg, 6%) and **5** (100 mg, 10%).

(e) *Heating at* 185° *in a sealed tube*

2 (1 g, 0.003 mol) was heated in a sealed tube at 185° for 8 hr. From the resulting reddish material was isolated **1** (520 mg, 52%). The remaining reaction mixture when subjected to preparative TLC using benzene as the developing solvnet afforded **3** (90 mg, 9%) and **4** (20 mg, 2%).

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References

1 Anjaneyulu A S R & Mallavadhani U V, *Indian J Chem*, **25B** (1986) 515.
2 Anjaneyulu A S R & Mallavadhani U V, *J chem Soc*, Perkin I, in press.
3 Anjaneyulu A S R, Rama Prasad A V & Sivakumar Reddi D, *Curr Sci*, **48** (1979) 300.
4 Anjaneyulu A S R, Mallavadhani U V & Venkateswarlu Y, *Indian J Chem*, **21B** (1982) 963.
5 Ballantyne M M, Murray R D H & McCabe P H, *Tetrahedron*, **27** (1971) 871.
6 Burling E D, Jefferson A & Scheinmann F, *Tetrahedron*, **21** (1965) 2653.

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Synthesis of 7,8-Dioxygenated Isoflavanones

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Facile synthesis of three 7,8-dimethoxy-(**4a, 4b** and **4c**)- and three 7,8-dihydroxy-(**9a, 9b** and **9c**)-isoflavanones according to the general method of Jain and Mehta [*J chem Soc Perkin-I*, (1986) 215] illustrate further usefulness of the method.

In order to study the scope of the new synthesis of isoflavanones developed in this laboratory[1-3], six different 7,8-dioxygenated isoflavanones have now been synthesized by this method. Although no 7,8-dioxygenated isoflavanone has been reported so far to occur in nature, it is likely that they are also present in plants because similar oxygenation pattern occurs in many related isoflavonoids[4].

First, three different 7,8-dimethoxyisoflavanones (**4a, 4b** and **4c**) were synthesized from the corresponding 2-hydroxy-3,4-dimethoxydesoxybenzoin (**1a**[5], **1b**[6] and **1c**[7] respectively). In each case, treatment of desoxybenzoin with one mol equivalent of ethoxymethyl chloride in the presence of dry potassium carbonate and acetone afforded corresponding α-hydroxymethyl derivative. Although the product from **1a** was the expected **2a** having chelated hydroxyl, those from **1b** and **1c** were found to be **3b** and **3c** respectively having ethoxymethoxy group in position-2 also. This protecting group had to be removed before cyclisation to give **2b** and **2c** respectively. Cyclisatiion of α-hydroxymethyldesoxybenzoins (**2a, 2b** and **2c**) in the presence of 2% aq. ethanolic sodium carbonate gave the corresponding methoxyisoflavanones (**4a, 4b** and **4c**) in overall yields of 57, 56 and 55% respectively.

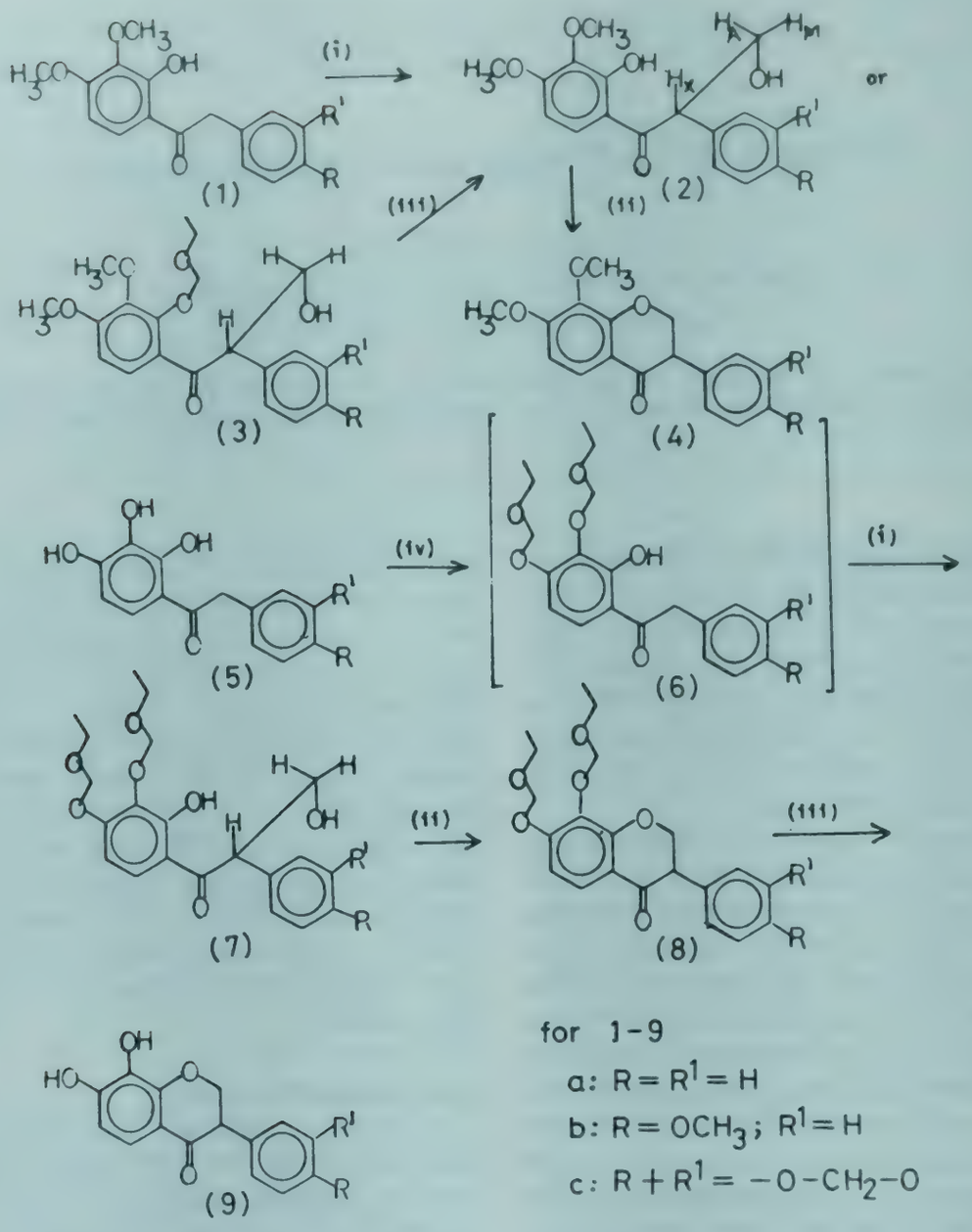
Next, 7,8-dihydroxyisoflavanones (**9a, 9b** and **9c**) were synthesised from corresponding 2,3,4-trihydroxydesoxybenzoins (**5a**[8], **5b**[1] and **5c**[9]) respectively. The first step was treatment of the desoxybenzoin with two mol equivalents of ethoxymethyl chloride in the presence of dry potassium carbonate and acetone in order to protect hydroxy groups in positions-3 and 4. Without isolating the products (**6a, 6b** and **6c** respectively), the reaction mixture was further treated with 1 mol equivalent of ethoxymethyl chloride at 60-70° when the corresponding α-hydroxymethyl derivatives (**7a, 7b** and **7c**) were obtained. Each of thse carbinols exhibited AMX pattern of signals for aliphatic protons in ^{1}H-NMR spectra and triplet of C_β and doublet of C_α protons atoms. Subsequently, these carbinols were cyclised with 2% aqueous alcoholic sodium carbonate to afford 7,8-*bis*-ethoxymethoxyisoflavanones (**8a, 8b** and **8c** respectively). Each of these products showed ABX pattern of isoflavanones besides the presence of two ethoxymethoxy signals (see Experimental). Final removal of the protecting groups with methanolic hydrogen chloride gave the desired 7,8-dihydroxyisoflavanones (**9a, 9b** and **9c** respectively) in overall yields of 45, 45 and 38 respectively. Thus, it is shown that original synthesis of Jain *et al.*[1-3] could well be adopted for 7,8-dioxygenated isoflavanones.

Experimental Procedure

All m.ps reported are uncorrected. Petrol used had boiling range 60-80°C. Silica gel was used for column chromatography and TLC. Solvent systems used for TLC were: (A) benzene, (B) benzene-ethyl acetate (95:5), (C) benzene-ethyl acetate (9:1), (D) benzene-ethyl acetate (8:2); R_f refers to TLC. UV spectra were recorded in MeOH on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm and log ε in parenthesis), IR spectra in either nujol or as KBr disc on a Shimadzu model 535 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a 90 MHz Perkin-Elmer model R-32 or a 200 MHz Jeol JNM FX-200 FT NMR instrument using TMS as internal standard; chemical shifts are recorded in δ (ppm) and *J* values in Hz.

Reaction of 2-*hydroxy*-3,4*dimethoxydesoxybenzoins* (**1a, 1b** *and* **1c**) *with ethoxymethyl chloride*

A solution of desoxybenzoin (**1a, 1b** or **1c**, 5 mmol) in dry acetone (100 ml) was treated with anhydrous K_2CO_3 (7.4 g, 50 mmol) followed by a solution of ethoxymethyl chloride (0.66 ml, 5 mmol) in acetone (8 ml). The resulting mixture was warmed initially at 40-50° for 10-15 min and then at 60-70°



for 1-9

a: $R = R^1 = H$

b: $R = OCH_3$; $R^1 = H$

c: $R + R^1 = -O-CH_2-O$

Reagents

(i) $CH_3CH_2\,O\,CH_2\,Cl$ (1 mol), K_2CO_3, Me_2CO, 60-70°

(ii) 2% Ag. Alcoholic Na_2CO_3

(iii) 10% MeOH-HCl

(iv) $CH_3-CH_2-O-CH_2-Cl$ (2 mol), K_2CO_3, Me_2CO, r.t.

with TLC monitoring. After the reaction was complete the reaction mixture was filtered hot, washed with acetone and the filtrate concentrated at room temperature. The residue was treated with crushed ice, the oily product extracted with ether and the ether residue subjected to column chromatography. It was eluted with petrol to remove impurities followed by petrol-ethyl acetate (99:1). The latter eluates afforded the corresponding α-hydroxymethyl erivatives (**2a**, **3b** and **3c**)

2-Hydroxy-α-hydroxymethyl-3,4-dimethoxydesoxybenzoin (**2a**)

It crystallised from ethyl acetate-petrol mixture as white needles (1.2 g, 79 yield), m.p. 98-100°; violet-green ferric reaction R_f (A) 0.45 (Found: C, 67.4; H, 5.9. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0); UV: 210(s) (4.46), 221(4.25) and 281(bs) (3.93); IR(KBr): 3550, 1660 and 1580; 90 MHz PMR($CDCl_3$): 2.62 (*bs*, 1H, alcoholic −OH), 3.38 (*m*, 7H, 2 × $-OCH_3$, C-H_A), 4.25 (*dd*, 1H, $J_{AM} = 11.3$, $J_{MX} = 8.2$, C-H_M),

4.80 (*dd*, 1H, J_{MX} 8.2, J_{AX} = 4.8, C-H_X), 6.42 (*d*, 1H, *J* = 9, C_5-H), 7.35 (*s*, 5H, $-C_6H_5$), 7.58 (*d*, 1H, *J* = 9, C_6-H), and 12.52 (*s*, 1H, chelated −OH); 50 MHz ^{13}C NMR($CDCl_3$): 53.3 (*q*, 2× $-OCH_3$), 57.0 (*d*, α-CH), 61.0 (*t*, β-CH_2OH), 94.0 (*d*, C-5), 106.0 (*s*, C-1), 126.85 (*d*, C-6), 127.52 (*d*, C-4′), 128.12 (*d*, C-3′,5′), 129.71 (*d*, C-2′,6′), 130.0 (*s*, C-1′), 132.2 (*s*, C-3), 153.0 (*s*, C-4), 171.48 (*s*, C-2), and 203.6 (*s* >C=O).

2-*Ethoxymethoxy*-α-*hydroxymethyl*-3,4,4′-*trimethoxydesoxybenzoin* (**3b**)

It was obtained as a viscous yellow oil (1.3 g, 78 yield), R_f (A) 0.40; UV: 215 and 272; IR: 340, 1670 and 1595; 90 MHz PMR($CDCl_3$): 1.41 (*t*, 3H, CH_3-CH_2-), 2.71 (*bs*, 1H, alcoholic −OH), 3.66 (*q*, 2H, CH_3-CH_2-O-), 3.71-3.84 (*m*, 10H, 3× $-OCH_3$, C-H_A), 4.24 (*dd*, 1H, J_{AM} = 11.3, J_{MX} = 8.2, C-H_M), 4.95 (*dd*, 1H, J_{MX} = 8.2, J_{AX} = 4.8, C-H_X), 5.33 (*s*, 2H, $-O-CH_2-O-$), 6.64 (*d*, 1H, *J* = 9, C_5-H), 6.80 (*d*, 2H, *J* = 10, $C_{3',5'}$-H), 7.24 (*d*, 2H, *J* = 10, $C_{2',6'}$-H), and 7.34 (*d*, 1H, *J* = 9, C_6-H).

2-*Ethoxymethoxy*α-*hydroxymethyl*-3,4-*dimethoxy*-3′,4′-*methylenedioxydesoxybenzoin* (**3c**)

It was obtained as a viscous oil (1.35 g, 77 yield); R_f (A) 0.40; UV: 207, 216 and 286; IR: 3465, 1660, 1600 and 1440; 90 MHz PMR($CDCl_3$): 1.87 (*t*, 3H, CH_3-CH_2-), 3.02 (*bs*, 1H, alcoholic OH), 3.68 (*q*, 2H, CH_3-CH_2-O-), 3.80 (*m*, 7H, 2× $-OCH_3$ and C-H_A), 4.20 (*dd*, 1H, J_{AM} = 11.3, J_{MX} = 8.2, C—H_M), 4.90 (*dd*, 1H, J_{MX} = 8.2, J_{AX} = 4.8, C-H_X), 5.21 (*s*, 2H, $-O-CH_2-O-$), 5.87 (*s*, 2H, $-O-CH_2-O-$), 6.65 (*d*, 1H, *J* = 9, C_5-H), 6.75 (*m*, 3H, $C_{2',5',6'}$-H), and 7.40 (*d*, 1H, *J* = 9, C_6-H).

Deprotection of 2-*ethoxymethoxy group in* **3b** *and* **3c**

Compounds (**3b** and **3c**) were separately heated with 10% methanolic hydrogen chloride (10 ml) for 10 min, cooled, diluted with water and extracted with ether. The ether solution gave 2-hydroxy-α-hydroxymethyl-3,4,4′-trimethoxydesoxybenzoin (**2b**) and 2-hydroxy-α-hydroxymethyl-3,4-dimethoxy-3′,4′-methylenedioxydesoxybenzoin (**2c**) respectively as oily liquids which were straightaway used in the next step.

Cyclisation of **2a, 2b** *and* **2c** *to form* 7,8-*dimethoxyisoflavanones* (**4a, 4b** *and* **4c** *respectively*)

To a solution of α-hydroxymethyldesoxybenzoin (**2a, 2b** or **2c**) (3.3 mmol) in ethanol (15 ml) was added 2% aq. alcoholic sodium carbonate (15 ml). The resulting mixture was refluxed for 25 min. Ethanol was distilled *in vacuo* and the residue purified by column chromatography to give cyclised products **4a-c**.

7,8-*Dimethoxyisoflavanone* (**4a**)

It was obtained as white crystals (600 mg, 66%, yield), m.p. 127-28°; R_f (C) 0.65 (Found: C, 71.9; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%); UV: 211 (4.85), 232 (bs) (4.11) and 281 (4.32); IR: 3110, 1700 and 1592; 90 MHz PMR ($CDCl_3$): 3.95 (*m*, 7H, 2× $-OCH_3$, C_3-H), 4.73 (*d*, 2H, *J* = 8, C_2-H), 6.7 (*d*, 1H, *J* = 9, C_6-H), 7.37 (*s*, 5H, $-C_6H_5$) and 7.80 (*d*, 1H, *J* = 9, C_5-H).

7,8,4′-*Trimethoxyisoflavanone* (**4b**)

It was obtained as white needles (700 mg, 68% yield), m.p. 168-69°; R_f (C) 0.60 (Found: C, 68.4; H, 5.8. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.8%); UV: 217 (4.27) and 275 (4.05); IR: 1605; 90 MHz PMR($CDCl_3$): 3.70 (*s*, 3H, $C_{4'}$-OCH_3), 3.90 (*m*, 7H, 2× $-OCH_3$ and C_3-H), 4.58 (*d*, 2H, *J* = 8, C_2-H), 6.67 (*d*, 1H, *J* = 9, C_6-H), 6.88 (*d*, 2H, *J* = 10, $C_{3',5'}$-H), and 7.75 (*d*, 1H, *J* = 9, C_5-H).

7,8-*Dimethoxy*-3′,4′-*methylenedioxyisoflavanone* (**4c**)

It was obtained as white crystals (700 mg, 65% yield), m.p. 112-13°; R_f (C) 0.60 (Found: C, 66.0; H, 5.2. $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.91%); UV: 211 (4.26), 229 (3.99) and 281 (4.04); IR: 1680 and 1695: 90 MHz PMR($CDCl_3$): 3.91 (*m*, 7H, 2× $-OCH_3$ and C_3-H), 3.66 (*d*, 2H, *J* = 8, C_2-H), 5.93 (*s*, 2H, $-O-CH_2-O-$), 6.67 (*d*, 1H, *J* = 9, C_6-H), 6.78 (*m*, 3H, $C_{2',5',6'}$-H), and 7.75 (*d*, 1H, *J* = 9, C_5-H).

Reaction of 2,3,4-*trihydroxydesoxybenzoins* (**5a, 5b** *and* **5c**) *with ethoxymethyl chloride*

A solution of **5a, 5b** or **5c** (10 mmol) in dry acetone (200 ml) was treated with anhydrous K_2CO_3 (7 g, 50 mmol), followed by a solution of ethoxymethyl chloride (2.64 ml, 20 mmol) in acetone (15 ml). The resulting mixture was stirred until TLC showed almost complete conversion (45 min) into a product considered to be 3,4-*bis*-ethoxymethoxy-2-hydroxydesoxybenzoin (**6a, 6b** or **6c** respectively). A further amount of ethoxymethyl chloride (1.32 ml, 10 mmol) was added to the above reaction mixture and the reaction warmed initially at 40-45° for 10-15 min and then at 60-70° until TLC showed almost complete conversion into another product. The reaction mixture was filtered hot and the filtrate concentrated at room temperature. The residue was treated with crushed ice, the oily product extracted with ether and the ether residue subjected to column chromatography. Elution with petrol-ethyl acetate

(19:1) afforded 2-hydroxymethyl derivatives (**7a, 7b** or **7c**).

3,4-*Bisethoxymethoxy*-2-*hydroxy*-α-*hydroxymethyldesoxybenzoin* (**7a**)

It was obtained as a viscous yellow oil (3 g, 77% yield), violet green ferric reaction; R_f (C) 0.39 (solvent C); UV: 213, 281 and 320; IR: 3430, 2900, 1650 and 1499; 90 MHz PMR($CDCl_3$): 1.16 (*t*, 6H, $2\times CH_3-CH_2-$), 2.98 (*bs*, 1H, exchangeable with D_2O, alcoholic $-OH$), 3.67 (*m*, 5H, $2\times -OCH_2-CH_3$ and C-H_A), 4.22 (*dd*, 1H, $J_{AM}=11.2$, $J_{MX}=8.4$, C-H_M), 4.77 (*dd*, 1H, $J_{MX}=8.2$, $J_{AX}=4.8$, C-H_X), 5.12 and 5.20 (2*s*, 2H each, $2\times -O-CH_2-O-$), 6.58 (*d*, 1H, $J=9$, C_5-H), 7.24 (*s*, 5H, C_6H_5-), 7.50 (*d*, 1H, $J=9$, C_6-H), and 12.64 (*s*, 1H, chelated $-OH$); 50 MHz ^{13}c NMR ($CDCl_3$): 15.9 (*q*, $2\times -CH_3$), 56.7 (*d*, α-CH), 65.49, 65.85 (2*t*, $2\times O-CH_2$), 66.04 (*t*, β-CH_2OH), 94.3, 97.41 (2*t*, $2\times -O-CH_2-O-$), 107.37 (*d*, C-5), 116.21 (*s*, C-1), 127.6 (*s*, C-6), 129.0 (*m*, C-3',4',5'), 130.0 (*d*, C-2',6'), 135.3 (*s*, C-1'), 137.5 (*s*, C-3), 158.0 (*s*, C-4), 159.2 (*s*, C-2) and 205.2 (*s*, >C=O).

3,4-*Bisethoxymethoxy*-2-*hydroxy*-α-*hydroxymethyl*-4'-*methoxydesoxybenzoin* (**7c**)

It was obtained as a viscous yellow oil (3.2 g, 76% yield); violet-green ferric reaction; R_f (C) 0.42; UV: 216, 275 and 323; IR: 3450(b), 1625 and 1600; 90 MHz PMR($CDCl_3$): 1.20 (*t*, 6H, $2\times CH_3-CH_2-$), 2.55 (*bs*, 1H, exchangeable with D_2O, alcoholic $-OH$), 3.64 (*q*, 4H, $2\times O-CH_2-CH_3$), 3.75 (*m*, 4H, $-OCH_3$ and C-H_A), 4.20 (*dd*, 1H, $J_{AM}=11.0$, $J_{MX}=8.0$, C-H_M), 4.70 (*dd*, 1H, $J_{MX}=8.0$ and $J_{AX}=4.8$, C-H_X), 5.18 and 5.24 (2*s*, 2H each, $2\times -OCH_2-O-$), 6.64 (*d*, 1H, $J=9$, C_5-H), 6.84 (*d*, 2H, $J=10$, $C_{3',5'}$-H), 7.20 (*d*, 2H, $J=10$, $C_{2',6'}$-H), 7.52 (*d*, 1H, $J=9$, C_6-H), and 12.64 (*s*, 1H, chelated $-OH$).

3,4-*Bisethoxymethoxy*-2-*hydroxy*-α-*hydroxymethyl*-3',4'-*methylenedioxydesoxybenzoin* (**7c**)

It was obtained as a viscous yellow oil (2.4 g, 69.3% yield); violet-green ferric reaction; R_f (C) 0.40; UV: 203, 215 and 278; IR: 3450 and 1625; 200 MHz PMR(CD_3COCD_3): 1.24 (*t*, 6H, $2\times CH_3-CH_2-$), 2.72 (*s*, 1H, alcoholic $-OH$), 3.86 and 4.02 (2*q*, 4H, $2\times -OCH_2-CH_3$), 4.20 (*dd*, 1H, $J_{AM}=11.2$ and $J_{AX}=4.8$, C-H_A), 4.42 (*dd*, 1H, $J_{AM}=11.0$, $J_{MX}=8.0$, C-H_M), 4.98 (*dd*, 1H, $J_{MX}=8.0$ and $J_{AX}=4.8$, C-H_X), 5.26 and 5.36 (2*s*, 2H each, $2\times -OCH_2O-$), 6.00 (*s*, 2H, O-CH_2-O cyclic), 6.84 (*d*, 1H, $J=9$, C_5-H), 7.04)*m*, 3H, $C_{2',5',6'}$-H), 7.96 (*d*, 1H, $J=9$, C_6-H), and 12.57 (*s*, 1H, chelated $-OH$).

Cyclisation of α-*hydroxymethyldesoxybenzoins* (**7a, 7b** *or* **7c**)

The above α-hydroxymethyl derivative (**7a, 7b** or **7c**) (2.5 mmol) was refluxed with ethanol (20 ml) and 4% aq. sodium carbonate (20 ml) for 35 min. Ethanol was distilled off *in vacuo* and the residue purified by column chromatography to give the following protected isoflavanones.

7,8-*Bisethoxymethoxyisoflavanone* (**8a**)

It was obtained as a viscous oil (600 mg, 59.1% yield); R_f (B) 0.45; UV: 228, 276 and 310; IR: 1680 and 1598; 90 MHz PMR($CDCl_3$): 1.21 (*t*, 6H, $2\times CH_3-CH_2-$), 3.73 (*q*, 4H, $2\times CH_3-CH_2-O-$), 3.93 (*t*, 1H, C_3-H), 4.70 (*d*, 2H, $J=8$, C_2-H), 5.21 and 5.31 (2*s*, 4H, $2\times OCH_2-O-$), 6.93 (*d*, 1H, $J=9$, C_6-H), 7.33 (*s*, 5H, C_6H_5) and 7.77 (*d*, 1H, $J=9$, C_5-H); 50 MHz ^{13}C NMR($CDCl_3$): 14.8 (*q*, $2\times -CH_3$), 51.6 (*d*, C-3), 64.5 (*t*, $2\times -CH_2-O$), 71.6 (*t*, C-2), 93.4 (*t*, $2\times O-CH_2-O$), 107.8 (*d*, C-6), 116.3 (*s*, C-10), 122.4 (*d*, C-5), 126.3 (*d*, C-4'), 127.5 (2*d*, C-3',5'), 129.3 (2*d*, C-2',6'), 133.5 (*s*, C-1'), 134.9 (*s*, C-8), 155.2 (*s*, C-7), 156.2 (*s*, C-9), and 198.58 (*s*, >C=O).

7,8-*Bisethoxymethoxy*-4'-*methoxyisoflavanone* (**8b**)

It was obtained as a viscous oil (850 mg, 85% yield); R_f (B) 0.50; UV: 218 and 275; IR: 1668 and 1660; 90 MHz PMR($CDCl_3$): 1.21 (*t*, 6H, $2\times CH_3-CH_2$), 3.75 (*m*, 8H, $2\times -OCH_2-CH_3$, $-OCH_3$ and C_3-H), 4.65 (*d*, 2H, $J=8$, C_2-H), 5.17 and 5.28 (2*s*, 4H, $2\times -OCH_2-O-$), 6.84 (*d*, 1H, $J=9$, C_6-H), 6.88 (*d*, 2H, $J=10$, $C_{3',5'}$-H), 7.02 (*d*, 2H, $J=10$, $C_{2',6'}$-H), and 7.70 (*d*, 1H, $J=9$, C_5-H).

7,8-*Bisethoxymethoxy*-3',4'-*methylenedioxyisoflavanone* (**8c**)

It was obtained as a viscous oil (690 mg, 66% yield); R_f (B) 0.40; UV: 220 and 280; IR: 1675, 1595 and 1490; 90 MHz PMR($CDCl_3$): 1.21 (*t*, 6H, CH_3-CH_2-), 3.75 (*m*, 5H, $2\times CH_3-CH_2O$ and C_3-H), 4.65 (*d*, 2H, $J=8$, C_2-H), 5.19 and 5.30 (2*s*, 2H each, $2\times -OCH_2O-$), 5.91 (*s*, 2H, $-OCH_2O-$ cyclic), 6.76 (*m*, 3H, $C_{2',5',6'}$-H), 6.88 (*d*, 1H, $J=9$, C_6-H), and 7.68 (*d*, 1H, $J=9$, C_5-H).

Deprotection of **8a, 8b** *or* **8c**

A solution of **8a, 8b** or **8c** (1.34 mmol) in methanol (20 ml) was warmed slowly with 10% methanolic hydrogen chloride (20 ml) for 10 min. The solution was concentrated to half the bulk, cooled, treated with equal amount of water and left overnight in the cold. The solid thus separated was collected, and crystallised to give the following products.

7,8-*Dihydroxyisoflavanone* (**9a**)

It crystallised from methanol as white plates (250 mg, 73% yield), m.p. 155-57°; R_f (C) 0.42 (Found: C, 70.4; H, 4.8. $C_{15}H_{12}O_4$ requires C, 70.3; H, 4.7%); UV: 211 (4.45), 237 (4.03) and 292 (4.14); IR: 3400 and 1680; 90 MHz PMR(CD_3COCD_3): 3.96 (*t*, 1H, C_3-H), 4.71 (*d*, 2H, $J=6$, C_2-H), 6.68 (*d*, 1H, $J=9$, C_6-H), 7.35 (*s*, 5H, C_6H_5-) and 7.45 (*d*, 1H, $J=9$, C_5-H); 50 MHz ^{13}C NMR (CD_3COCD_3): 52.8 (*d*, C-3), 73.3 (*t*, C-2), 112.0 (*d*, C-6), 117.0 (*s*, C-10), 121.0 (*d*, C-5), 121.9 (*d*, C-3′,4′,5′), 130.0 (*d*, C-2′,6′), 133.3 (*s*, C-1′), 137.3 (*s*, C-8), 153.0 (*s*, C-7), 154.0 (*s*, C-9), and 210.0 (*s*, $>C=O$).

7,8-*Dihydroxy*-4′-*methoxyisoflavanone* (**9b**)

It crystallised from chloroform as white plates (235 mg, 69.2% yield), m.p. 168-69°; R_f (C) 0.40 (solvent C) (Found: C, 66.9; H, 4.6. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%); UV: 218 (4.53), 238 (4.25) and 292 (4.22); IR: 3350, 1660, and 1565; 200 MHz PMR(CD_3COCD_3): 380 (*m*, 4H, $-OCH_3$ and C_3-H), 4.78 (*d*, 2H, $J=8$, C_2-H), 6.66 (*d*, 1H, $J=9$, C_6-H), 6.94 (*d*, 2H, $J=10$, $C_{3'5'}$-H), 7.26 (*d*, 2H, $J=10$, $C_{2',6'}$-H), and 7.38 (*d*, 1H, $J=9$, C_5-H).

7,8-*Dihydroxy*-3′,4′-*methylenedioxyisoflavanone* (**9c**)

It crystallised from chloroform as white plates (330 mg, 63% yield); m.p. 178-79°; R_f (C) 0.40 (solvent C); (Found C, 64.2; H, 4.0. $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0%); UV: 203 (4.58), 214 (4.51) and 285 (4.19); IR: 3500 and 1663; 200 MHz PMR(CD_3COCD_3): 2.80 (*t*, 1H, C_3-H), 4.75 (*d*, 2H, $J=8$, C_2-H), 6.00 (*s*, 2H, $-OCH_2O-$), 6.75 (*d*, 1H, $J=9$, C_6-H), 6.90 (*m*, 3H, $C_{2',5',6'}$-H) and 7.50 (*d*, 1H, $J=9$, C_5-H).

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References

1 Jain A C & Sharma A, *Indian J Chem*, **23B** (1984) 451.
2 Jain A C & Sharma A, *Chem Commun*, (1985) 338.
3 Jain A C & Mehta A (nee Sharma), *J chem Soc Perkin I*, (1986) 215.
4 Dewick P M, in *The flavonoids: Advances in research*, edited by J.B. Harborne & T.J. Mabry (Chapman and Hall, London), 1982, pp. 635.
5 Dass I, Narasimhachari N & Seshadri T R, *Proc Indian Acad Sci*, **37A** (1953).
6 Kametani T, Okubo K, Noguchi I & Manske R H F, *Tetrahedron Lett*, (1965) 3345.
7 Fukui K & Matsumoto T, *Bull chem Soc Japan*, **38** (1965) 612.
8 Karmarkar S S, *J scient ind Res*, **30B** (1961) 3348.
9 Kukla A S & Seshadri T R, *Tetrahedron*, **18** (1962) 1443.

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Studies in Synthesis of Furocoumarins : Part XXVIII†—Synthesis of Difuranocoumarins

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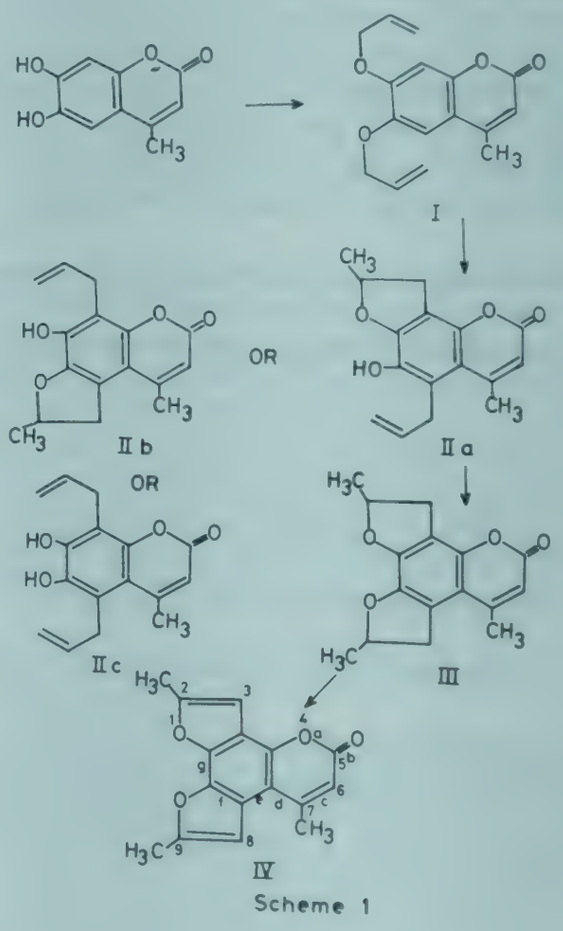
6,7-Diallyloxy-4-methylcoumarin(I) on Claisen migration gives 8-allyl-9-hydroxy-2,7-dimethyldihydrofurano[2,3-*h*] [1]-benzopyran-5(*H*)-one (IIa). The structure of IIa has been confirmed by spectral data (UV, PMR) and IIa is found to be identical (m.m.p., co-TLC) with a product synthesised unambiguously starting from 6,7-diacetoxy-4-methylcoumarin. Product (IIa) on cyclisation with H_2SO_4 gives a tetrahydrodifurano derivative (III) which on dehydrogenation over 10 % Pd/C furnishes the difurano derivative (IV). Structures of all these compounds have been confirmed by their PMR spectra.

For sometime we have been interested in the synthesis of various difurocoumarins[1,2]. Presently we have synthesised some diallyloxycoumarins and studied their Claisen rearrangement.

6,7-Diallyloxy-4-methylcoumarin (I), prepared by allylation of 6,7-dihydroxy-4-methylcoumarin, on Claisen rearrangement in N,N-dimethylaniline gave a product which could have either structure IIa or IIb. The possibility of structure (IIc) was ruled out on the basis of PMR spectrum which indicated the presence of dihydrofurano ring system and free allyl group. It also did not develop green colouration with neutral ferric chloride solution. The identity of IIa (Scheme 1) was finally confirmed by an unambiguous synthesis as follows:

6,7-Diacetoxy-4-methylcoumarin (V), obtained by acetylation of 6,7-dihydroxy-4-methylcoumarin, on condensation with one mol of allyl bromide (K_2CO_3-acetone method) gave 6-acetoxy-7-allyloxy-4-methylcoumarin (VI). The structure of VI was assigned on the basis of analogy of allylation of 6,7-diacetoxycoumarin[3]. VI on Claisen rearrangement in boiling N,N-dimethylamiline gave 8-allyl-6,7-dihydroxy-4-methylcoumarin (VII), which on cyclisation with 80 % sulphuric acid furnished 9-hydroxy-2,7-dimethyldihydrofurano[2,3-*h*][1]-benzopyran-5(*H*)-one (VIII). Compound (VIII) on condensation with allyl bromide led to 2,7-dimethyl-9-allyloxy-dihydrofurano [2,3-*h*] [1]-benzopyran-5(*H*)-one (IX), which on Claisen rearrangement in boiling N,N-dimethylaniline gave the product which was identical (m.m.p., co-TLC) with IIa (Scheme 2). Product (IIa) on cyclisation with 80% sulphuric acid gave 2,7,9-trimethyl-2,3,8,9-tetrahydrodifurano [2,3-*h*: 2′,3′-*f*][1]-benzopyran-5(*H*)-one (III), which on dehydrogenation with palladised charcoal afforded 2,7,9-trimethyldifurano [2,3-*h*: 2′,3′-*f*][1]-benzopyran-5(*H*)-one (IV).



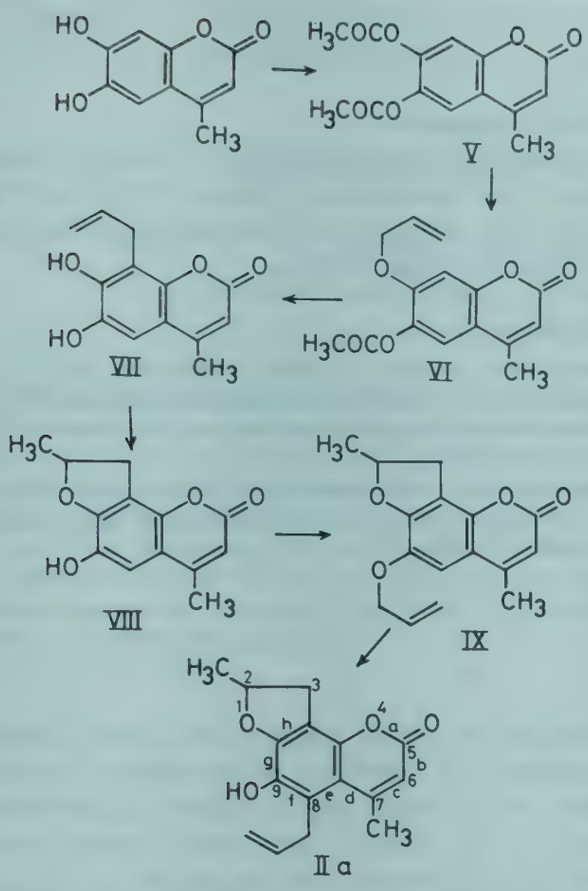
Scheme 1

Experimental Procedure

6,7-*Diallyloxy*-4-*methylcoumarin* (*I*)[3]

A mixture of 6,7-dihydroxy-4-methylcoumarin (4.0g), allyl bromide (4.2 ml) and anhydrous potassium carbonate (16g) in dry acetone (200 ml) was

†Part XXVII : Desai S M & Trivedi K N, *Indian J Chem*, **24B** (1985) 47



Scheme 2

refluxed for 10 hr on a water-bath, concentrated and poured into water. The solid obtained was filtered, washed with aq sodium hydroxide and crystallised from benzene, m.p. 102°, yield 3.4 g (Found : C, 71.0; H, 6.2. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8 %).

8-Allyl-9-hydroxy-2,7-dimethyl-dihydrofurano [2,3-h] (1) - benzopyran-5(H)-one (IIa)

Compound (I, 2g) was refluxed with N,N-dimethylaniline (10 ml) for 5 hr and poured into concentrated hydrochloric acid containing crushed ice. The reaction mixture was extracted with ether, etheral layer shaken with aq. sodium hydroxide, the alkaline layer separated and acidified with conc. hydrochloric acid. The separated product was purified by column chromatography using benzene as an eluent and recrystallised from benzene, m.p. 144°; yield 1.0 g (Found : C, 70.2; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8 %); PMR ($CDCl_3$/TMS) : δ 1.5 (3H, *d*, J= 7Hz, C_2-CH_3), 2.8(3H, *s*, C_7-CH_3), 3.0 (1H, *dd*, J= 18, 8Hz, C_3-H), 3.4 (1H, *dd*, J= 18, 8 Hz, C_3-H), 3.75 (2H, *m*, $-CH_2$-$CH=CH_2$), 5.0 (3H, *m*, $-CH_2$-$CH=CH_3$) and C_2-H), 5.6 (1H, *m*, $-CH_2$-$CH=CH_2$), 6.0(1H, *s*, C_6-H); UV(MeOH)[4] : λ_{max} 340 nm (log ε 5.2); 1*M* NaOH : λ_{max} 400 nm (log ε 2.4).

2,7,9-Trimethyl-2,3,8,9-tetrahydrodifurano[2,3,-h : 2',3'- f][1]-benzopyran-5(H)-one (III)

Compound (IIa, 1g) was triturated with conc. sulphuric acid (5 ml) and then heated on a water-bath for 10 min. The mixture was poured onto crushed ice, the separated product filtered off and washed with aq. sodium hydroxide. It was purified by column chromatography using benzene as an eluent and then recrystallised from benzene, m.p. 182°, yield 0.7g (Found : C, 70.4; H, 6.0. $C_{26}H_{16}O_4$ requires C, 70.6; H, 5.8 %); PMR ($CDCl_3$/TMS) : δ 1.5(6H, *d*, J= 7Hz, C_2-CH_3 and C_3-CH_3), 2.4(3H, *s*, C_7-CH_3), 2.8-3.8 (4H, *m*, C_3-CH_2- and C_8-CH_2-), 5.1 (2H, *m*, C_2-H and C_9-H), 6.0 (1H, *s*, C_6-H).

2,7,9-Trimethyl-difurano[2,3-h; 2',3'-f][1]-benzopyran-5(H)-one (IV)

A mixture of III (0.5g) and 10 % pd/C (1g) was refluxed in diphenyl ether (5-6 ml) for 24 hr. The reaction mixture was filtered hot and the solvent removed by steam distillation. The product was purified by preparative TLC and crystallised from benzene, m.p. 212°; yield 0.2g (Found : C, 71.2; H, 4.2. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.4 %). It showed yellow fluoroscence in UV light; PMR ($CDCl_3$/TMS): δ 2.5 (6H, *s*, C_2-CH_3 and C_9-CH_3), 2.6(3H, *s*, C_7-CH_3), 6.2(1H, *s*, C_6-H), 6.8(2H, *s*, C_3-H and C_8-H).

6,7-Diacetoxy-4-methyl coumarin (V)

6,7-Dihydroxy-4-methylcoumarin (4g) was acetylated (anhydrous sodium acetate/Ac_2O). Usual work-up afforded V, which was crystallised from benzene, m.p. 154°; yield 4.2g (Found : C, 60.7; H, 4.1. $C_{14}H_{12}O_6$ requires C, 60.8; H, 4.2 %).

7-Allyloxy-6-acetoxy-4-methylcoumarin (VI)

Allylation of V (2.7g) with allyl bromide (1.2 ml) by anhydrous K_2CO_3-acetone method afforded VI, after usual work-up. VI was crystallised from benzene, m.p. 142°; yield 1.9g (Found : C, 65.2; H, 5.0. $C_{15}H_{14}O_5$ requires C, 65.6; H, 5.1 %).

8-Allyl-6,7-dihydroxy-4-methylcoumarin (VII)

Compound (VI, 2g) was refluxed with dimethylaniline (10 ml) for 5 hr and poured into concentrated hydrochloric acid containing crushed ice. The reaction mixture was extracted with ether, the ethereal layer shaken with aq. sodium hydroxide, the alkaline layer separated and acidified with conc. hydrochloric acid to yield VII. The separated product was purified by column chromatography using benzene as an eluent and recrystallised from benzene, m.p. 225°; yield 1g (Found : C, 66.8; H, 5.0. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.1 %).

9-Hydroxy-2,7-dimethyl-dihydrofurano[2,3-h][1]-benzopyran-5(H)-one (VIII)

Compound (VII, 1g) was triturated with conc.

sulphuric acid (5 ml) and then heated for 10 min in a water-bath. The mixture was poured onto crushed ice, the separated product filtered and crystallised from benzene, m.p. 201°, yield 0.6g (Found : C, 67.6; H, 5.3. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.1 %); PMR (DMSO-d_6/TMS) : δ 1.4(3H, *d*, *H*= 7Hz, C_2-CH_3), 2.4(3H, *s*, C_7-CH_3), 2.8-3.2 (2H, *m*, C_3-H_2), 5.1 (1H, *m*, C_2-H), 6.1(1H, *s*, C_6-H), 6.95 (1H, *s*, C_8-H).

9-Allyloxy-2,7-dimethyl-dihydrofurano[2,3-*h*]-(1) *benzopyran-5(H)-one* (*IX*)

A mixture of VIII (2.5g), anhydrous K_2CO_3 (8g) and allyl bromide (1.2 ml) was refluxed for 8 hr in dry acetone (150 ml); usual work-up afforded IX which was washed with aq. NaOH and crystallised from benzene, m.p. 130°, yield 1.5 g (Found : C, 70.9; H, 5.7. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8 %).

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References

1 Desai S M & Trivedi K N, *Indian J Chem*, **24B** (1985) 47.
2 Sanghvi K P & Trivedi K N, *J Indian chem Soc*, **56** (1979) 56.
3 Ahluwalia V K, Sachdev G P & Seshadri T R, *Indian J Chem*, **7** (1969) 59.
4 Dakhovlinova L I, Avramenke L G, Skylar Yu E & Pimenov M G, *Khim Prir Soedin*, **11** (1975) 512; *Chem Abstr*, **83** (1975) 203751.

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Mass Spectra of α-Phenylcinnamonitriles†

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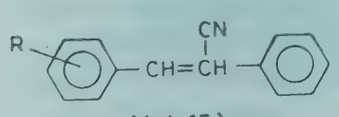
The electron impact fragmentation pathways of a number of α,β-unsaturated nitriles have been studied with the help of accurate mass and metastable peak measurements and labelling studies. The fragmentation of α-phenylcinnamonitrile occurs via rearrangement and cyclisation followed by loss of $\cdot CH_3$, $\cdot CH_2CN$ or HCN. The chlorinated derivatives fragment mainly by successive losses of two radicals such as ·H and ·Cl violating the 'even electron rule'. Under negative ionization conditions apart from abundant $M^{-\cdot}$ ions, $(M-H)^-$, $(M-2H)^-$ and $(M-4H)^-$ ions are observed. In the chloro compounds analogous fragmentation leads to $(M-HCl)^-$ ions. The *o*-chloro derivatives are characterised by more abundant $(M-Cl)^+$ or $(M-HCl)^-$ ions than the *m*- and *p*-chloro compounds in their positive or negative ion spectra respectively. Saturation of the double bond completely changes the fragmentation modes under both positive and negative ionization conditions.

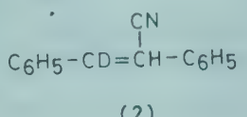
Substituents have a pronounced effect on the electron impact fragmentation pathways of aromatic α,β-unsaturated carbonyl compounds[1-4]. No such systematic studies have been carried out on the mass spectra of conjugated nitriles even though the mass spectra of a few of them have been reported[5-9]. Further, in continuation of our earlier work on the mass spectra of α,β-unsaturated carbonyl compounds[4,10]; we undertook a study on the fragmentation modes of a number of α-phenylcinnamonitriles under both positive and negative ionization conditions. The results of this study involving deuterium and ^{13}C labelling, accurate mass and metastable peak measurements are presented in this paper.

Positve ion spectra

The ion abundances in the 70 eV positive ion electron impact (EI) spectra of α-phenylcinnamonitriles (**1-15**) and the dihydro derivatives **16** and **17** are given in Table 1. Table 2 gives the high resolution mass spectral (HRMS) data of **1-3.** Under EI α-phenylcinnamonitrile showed the characteristic fragmentation patterns of both stilbene[6] and conjugated nitriles[5,7] (Scheme 1). The absence of these



(1,4,15)



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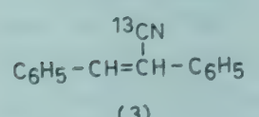
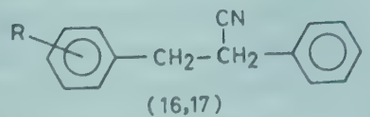
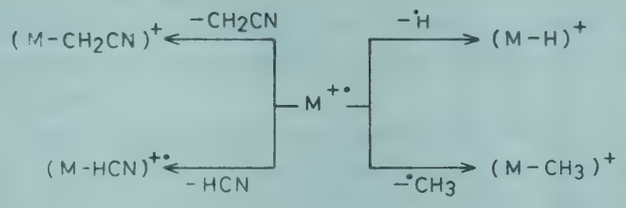


(3)



(16,17)



Scheme 1

fragmentation pathways in the saturated analogues **16** and **17** suggested that like stilbenes these conjugated nitriles also undergo fragmentation from the rearranged molecular ions[11]. Isomerization from (*Z*) to (*E*) and rearrangement to 9-methyl-9-cyano- and 9-cyanomethyl-fluorenes via 9-cyano-9,10-dihydrophenanthrene followed by loss of $\cdot CH_3$ and $\cdot CH_2CN$ can explain the formation of the ions at *m/z* 190 and 165 in the case of **1** (Scheme 2). In the spectrum of the ^{13}C nitrile (**3**) these peaks appeared at *m/z* 191 and 165 supporting the above pathway.

Hydrogen and carbon scrambling is reported to occur in stilbene molecular ion before it loses ·H and $\cdot CH_3$ radicals[12]. In the spectrum of the deuterated α-phenylcinnamonitrile (**2**), the ratios $(M-CH_3)^+/(M-CH_2D)^+$ and $(M-CH_2CN)^+$ varied between 2.8-3.3 and 1.8-1.4 at 20 and 70 eV respectively thereby suggesting that hydrogen scrambling also occurs in α-phenylcinnamonitrile before it loses $\cdot CH_3$ and $\cdot CH_2CN$.

Substitution of the aromatic ring with chlorine considerably altered these fragmentation modes. Loss of chlorine radical took precedence over other fragmentation pathways. As a result elimination of $\cdot CH_3$, $\cdot CH_2CN$ and HCN was suppressed. The variation in the ratio $(M-Cl)^+/M^{+\cdot}$ with electron energy for different chloro derivatives is shown in

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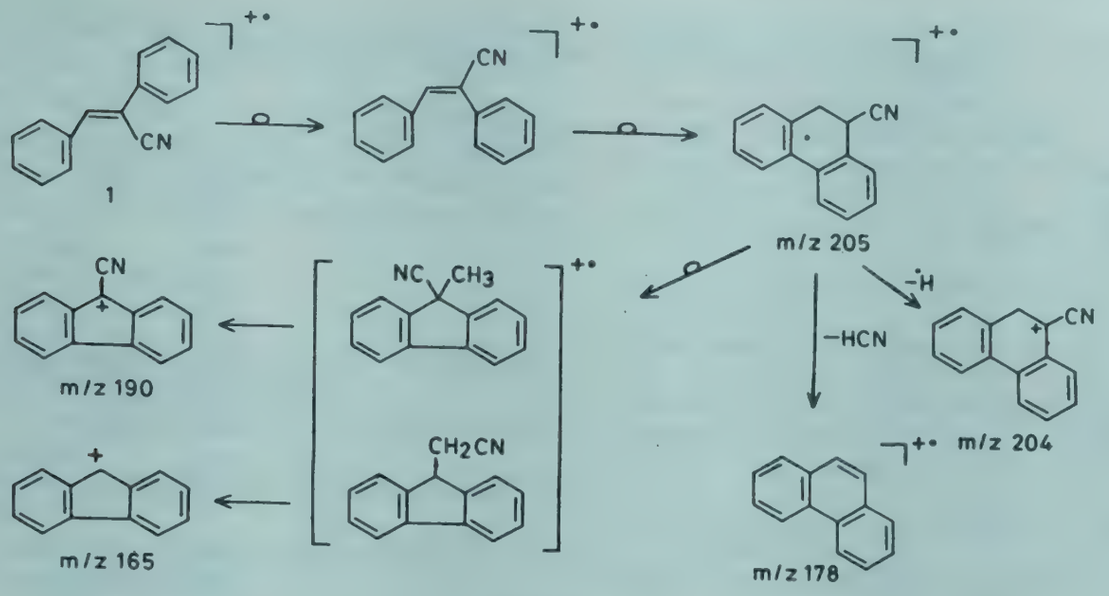
Table 1—Ion Abundances (%) in the Positive Ion EI Spectra of **1-17**

Compd	R	M wt	Ion (*m/z*)										
			$M^{+\cdot}$	$(M-H)^+$	$(M-CH_3)^+$	$(M-HCN)^+$	$(M-CH_2CN)^+$	$(M-R)^+$	$(M-RH)^+$	178	177	165	Others
1	H	205	100	74	36	16	10	—	—	16	21	10	176(16), 151(8)
2	—	206	100	83	26, 10[a]	12	5, 4[b]	—	—	17	14	4	176(6), 152(5)
3	—	206	100	91	36	6	10[c]	—	—	17	19	10	176(14), 151(7)
4	3-F	223	100	57	23	15	9	4	15	3	4	—	195(12)
5	2-Cl	239	39	4	3	2	—	100	34	5	23	—	176(16), 175(6)
6	3-Cl	239	60	11	5	2	1	100	42	5	22	—	176(18), 175(7)
7	4-Cl	239	71	8	4	2	1	100	45	7	24	—	176(18), 175(7)
8	2-Cl, 4-Cl	273	51	3	2	2	—	54	20	—	7	—	203(100), 202(36)
9	3-Cl, 4-Cl	273	84	9	6	2	1	57	33	—	8	—	203(100), 202(32)
10	4-OH	221	100	36	12	5	3	8	7	3	7	17	202(19), 176(3)
11	4-OMe	235	100	21	7	1	—	13	7	—	9	36	219(9), 190(19)
12	3-OMe, 4-OH	251	100	6	7	3	—	9	7	11	7	8	208(16), 190(52)
13	3-OH, 4-OMe	251	100	5	11	—	—	9	4	17	13	15	208(30), 190(73)
14	3-OMe, 4-OMe	265	100	—	18	—	—	5	—	15	12	10	222 (14), 190(31)
15	2-OH, 5-Br	299	45	100	—	3	—	—	10	—	—	16	110(13)
16	H	207	10	—	—	—	—	—	—	—	—	—	91(100), 116(2)
17	2-Cl	241	15	—	—	—	—	—	—	—	—	—	125(100), 116(6)

[a]$(M-CH_2D)^+$; [b]$(M-CHDCN)^+$; [c]$(M-CH_2{}^{13}CN)^+$

Table 2—High Resolution Mass Spectral (HRMS) Data of **1-3**

Compound **1**			Compound **2**			Compound **3**		
Composition	Mass		Composition	Mass		Composition	Mass	
	Obsd	Calc		Obsd	Calc.		Obsd	Calc.
$C_{15}H_{11}N$	205.0886	205.0891	$C_{15}H_{10}ND$	206.0947	206.0954	$C_{14}H_{11}{}^{13}CN$	206.0895	206.0924
$C_{15}H_{10}N$	204.0819	204.0813	$C_{15}H_9ND$	205.0886	205.0876	$C_{14}H_{10}{}^{13}CN$	205.0818	205.0846
$C_{14}H_8N$	190.0658	190.0656	$C_{14}H_7ND$	191.0707	191.0719	$C_{13}H_8{}^{13}CN$	191.0681	191.0689
			$C_{14}H_8N$	190.0671	190.0656			
$C_{14}H_{10}$	178.0776	178.0782						
$C_{14}H_8$	176.0637	176.0626						
$C_{13}H_9$	165.0704	165.0704	$C_{13}H_9$	165.0680	165.0704	$C_{13}H_9$	165.0704	165.0704
			$C_{13}H_8D$	166.0783	166.0764			



Scheme 2

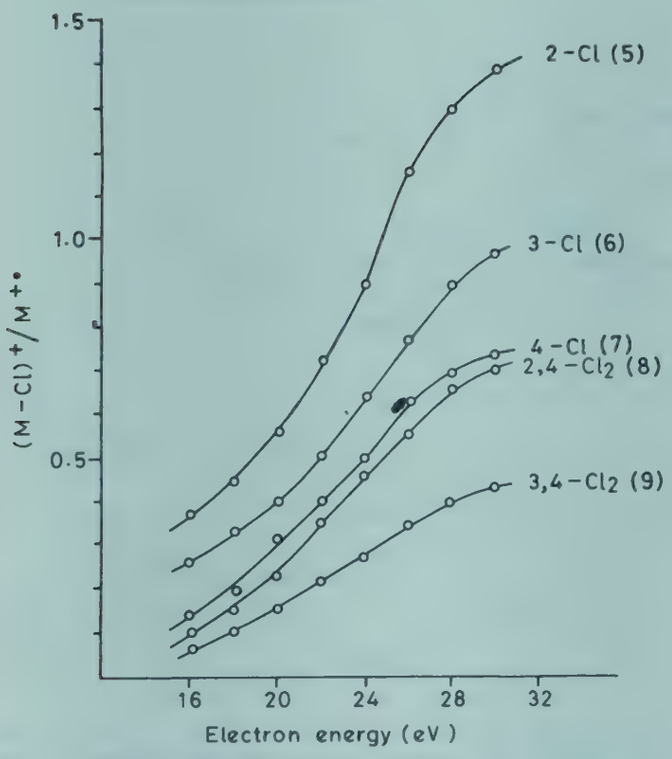


Fig. 1—Variation of $(M-Cl)^+/M^{+\cdot}$ ion with electron energy for **5-9**

Fig. 1. The $(M-Cl)^+$ ion abundance increased in the order $p<m<o$ as observed in the case of chlorine substituted cinnamic acids[3].

Metastable peaks were observed by high voltage scan for the stepwise loss of ·Cl and ·H from M^+. In the high voltage scan spectrum of the ion at *m/z* 203 corresponding to loss of HCl from M^+ in the case of **5**, the major contribution was from $(M-Cl)^+$ ion (*m/z* 204, 88% and *m/z* 239, 12%). The dichloro derivatives **8** and **9** also showed stepwise loss of two chlorine radicals giving rise to the ions at *m/z* 238 and 203. Successive loss of two radicals is a violation of the 'even electron rule'[13]. However, chloroaromatics are known to violate this rule because of the stability of the resulting aromatic cations[13].

The bromohydroxy compound **15** was characterised by a base peak corresponding to $(M-H)^+$ ion. The *m/z* 165 ion, absent in the spectra of the halogenated derivatives, was observed in the spectra of the hydroxy and methoxy substituted compounds.

Saturation of the double bond changed the fragmentation pattern completely. In the dihydro derivatives **16** and **17** the base peak corresponded to the simple cleavage product, the tropylium ion.

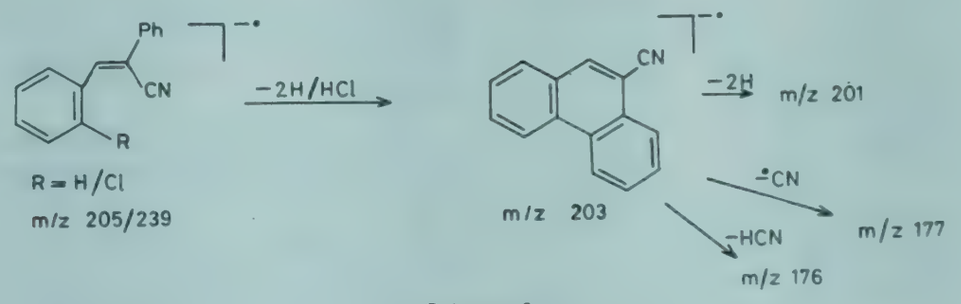
Negative ion spectra

The ion abundances in the negative ion spectra of **1-17** are given in Table 3. Nitriles are known to give abundant $(M-1)^-$ ions in their negative ion spectra[14]. However, most of the ion current in the negative ion spectrum of the parent nitrile **1** is carried by the $M^{-\cdot}$ as the captured electron is well stabilised by the conjugated system. Losses of ·H, 2H, 4H and (2H + HCN) give rise to minor fragment ions. An increase in aromaticity via cyclisation leading to the formation of 9-cyanophenanthrene appears to be the driving force for fragment formation (Scheme 3). In support of this is the fact that these ions were also observed in the negative ion spectrum of 9-cyanophenanthrene [*m/z* 203 (100), 201 (24.7), 177 (3.1) and 176 (2.1)].

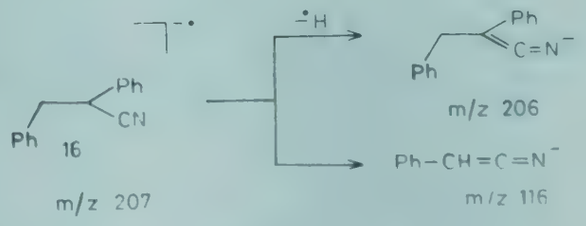
It may be noted here that among the chloro derivatives which fragment in an analogous manner, the *ortho*-derivative was characterised by abundant $(M-Cl)^-$ and $(M-HCl)^-$ ions while these ions were less important in the case of *meta*- and *para*-compounds.

Table 3—Ion Abundances (%) in the Negative Ion Spectra of **1-17**

Compd	$M^{-\cdot}$	$(M-H)^-$	$(M-2H)^-$	$(M-R)^-$	$(M-RH)^-$	$(M-2H-RH)^-$	$(M-CH_3)^-$	Others
1	100	4	5	—	—	—	—	201(2), 176(2)
2	100	13	2	—	—	—	—	202(1), 177(1)
3	100	12	1	—	—	—	—	—
4	100	4	12	—	—	8	—	194(2)
5	76	33	5	66	100	74	15	273(8), 177(13), 176(21)
6	100	3	3	4	8	10	1	273(2), 177(2), 176(2)
7	100	3	3	3	7	10	—	273(3), 177(2), 176(2)
8	100	7	3	27	32	—	—	308(27), 202(19), 201(34)
9	100	—	—	—	3	—	—	308(2), 201(8)
10	58	100	6	—	—	—	—	192(2), 190(3)
11	100	—	—	—	—	—	89	190(2)
12	100	10	—	—	—	—	16	235(7), 207(5)
13	11	2	—	—	—	—	100	—
14	23	—	—	—	—	—	100	249(12), 235(7)
15	52	100	28	12	12	—	—	378(22), 190(7)
16	—	2	—	—	—	—	—	116(100), 114(14)
17	—	2	—	3	4	—	—	116(100), 114(4)



Scheme 3



Scheme 4

The spectra of the hydroxy and methoxy compounds were characterised by the base peaks corresponding to $(M-H)^-$ or $(M-CH_3)^-$ ions due to stability of the resulting phenoxide ion. This explains why the most abundant ion in the 3-methoxy-4-hydroxy derivative **12** was $M^{-\cdot}$, while in the isomeric 3-hydroxy-4-methoxy derivative **13** the base peak corresponded to $(M-CH_3)^-$ ion. An abundant $(M-H)^-$ ion was also observed in **12**. It may be recalled that there was no difference in the positive ion spectra of **12** and **13** (cf. Table 1).

As observed under positive ion conditions, saturation of the double bond remarkably changed the negative ion spectra. No $M^{-\cdot}$ ion was observed in the case of **16** and **17**. The molecular weight was indicated only by a small $(M-H)^-$ ion, while the base peaks in the spectra of **16** and **17** corresponded to the simple cleavage product at *m/z* 116 (Scheme 4) which is the fragment complementary to the tropylium ion observed in the positive ion spectrum at *m/z* 91 or 125 in **16** and **17** respectively (cf. Table 1).

In conclusion, the negative ion spectra of these molecules are simpler than the positive ion spectra and also indicative of the substitution pattern of the molecule as the spectra vary with the nature of the substituent on the aromatic ring.

Experimental Procedure

The α-phenylcinnamonitriles (**1-15**) were prepared from the respective benzaldehyde and benzyl cyanide by reported procedure[15]. The ^{13}C labelled compound **3** was prepared from benzaldehyde and $PhCH_2{}^{13}CN$ which was obtained by reaction of benzylchloride and $K^{13}CN$. The dihydro derivatives **16** and **17** were obtained by sodium borohydride reduction of the corresponding cinnamonitriles.

The mass spectra were recorded on a Jeol D-300 mass spectrometer having a JMS 2000 data system. The ion source conditions were: electron energy, 70 eV; emission current, 100 μA (positive)

and 300 μA (negative); and temperature, 150°C. The samples were introduced through the direct inlet system. The HRMS data were obtained on a D-300 mass spectrometer using the data system at a resolution of 5000. The metastable spectra were measured on a Jeol OISG-2 mass spectrometer by high voltage scan.

References

1 Schaldach B, Grotemeyer B, Grotemeyer J & Grutzmacher H F, *Org Mass Spectrom*, **16** (1981) 410.

2 Rouvier H, Madina H & Cambon A, *Org Mass Spectrom*, **11** (1976) 800.

3 Schaldach B & Grutzmacher H F, *Org Mass Spectrom*, **15** (1980) 175.

4 Madhusudanan K P, Mittal S, Durani S & Kapil R S, *Org Mass Spectrom*, **20** (1985) 215.

5 Williams D H, Cooks R G, Bowie J H, Madsen P, Schroll G & Lawesson S D, *Tetrahedron*, **23** (1967) 3173.

6 Gusten H, Klasinc L, Kramer V & Marsal J, *Org Mass Spectrom*, **8** (1974) 323.

7 Carbone D, Fisichella S, Ochipinti S & Scarlata G, *J heterocycl Chem*, **19** (1982) 1505.

8 Wils E R J & Hulst A G, *Frasenius Z Anal Chem*, **320** (1985) 357.

9 Wang C B, Her G R & Watson J T, *Org Mass Spectrom*, **18** (1983) 457.

10 Madhusudanan K P, Akhtar M S, Seth M & Bhaduri A P, *Indian J Chem*, **25B** (1986) 915.

11 Bowie J H & White P Y, *Aust J Chem*, **24** (1971) 205.

12 Bowie J H & White P Y, *Org Mass Spectrom*, **6** (1972) 135.

13 Karni M & Mandelbaum A, *Org Mass Spectrom*, **15** (1980) 53.

14 Bush K L, Parker C E & Harvan D J, *Appl Spectroscopy*, **35** (1981) 85.

15 Wawzonek S & Smolin E M, *Org Synth*, **29** (1949) 83.

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Chemistry of Herbacin & New Unusual Sterols from Marine Sponge *Dysidea herbacea*†

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Three new compounds A, B and C have been isolated from the *n*-hexane extract of marine sponge *Dysidea herbacea*. Compound A, named herbacin (I) is a new furanosesquiterpene, which undergoes rearrangement to a Δ^3-butenolide(III), via the unstable keto-aldehyde (II) during *m*-CPBA oxidation. The structures of compounds B and C have been elucidated by a combination of GC-MS and high resolution PMR spectra as 24(*R*+*S*)-isopropenylcholest-7-en-3β-ol (IV) and 24ξ-isopropenylcholest-7-ene-3β,6α-diol (V), respectively having the unusual feature of a Δ^7 with C-24 isopropenylation, a combination which has not been so far being encountered in sterols from marine sources.

We have reported earlier the structure and stereochemistry of a new furanosesquiterpene, herbacin (I), from the marine sponge *Dysidea herbacea*[1]. Further chemical examination of the *n*-hexane extract of the sponge gave us an opportunity to explore the chemistry of I (compound A) as well as to isolate the minor constituents (compounds B and C). In this paper, we describe the oxidative rearrangements of I (isolated from *n*-hexane eluates of the silica gel column) and the structure elucidation of compounds B and C which were isolated from the subsequent chromatographic fractions as the unusual steroids IV and V respectively.

Chemistry of herbacin (I)

Catalytic hydrogenation of the isolated Δ^1 of I over 10% Pd/C failed to give the expected known compound, microcionin[2]. Drieding models showed crowding of Δ^1 with 13-Me in the rings A/B having *cis* disposition and hence failure to undergo hydrogenation. It did not undergo epoxidation either (*m*-CPBA/$CHCl_3$, ice bath, 24 hr), even after the furan ring got oxidised. The oxidation product (II), isolated in equimolar yield by working-up under cold conditions was very unstable. It was a ene-dione, exhibiting a broad UV maximum at 228 nm (ε = 14,000) due to the two competing carbonyl functions. Of these two, one was part of a six-membered ring (ν_{max} 1680 cm^{-1}) and the other was an aldehyde (ν_{max} 1670 cm^{-1}; PMR: δ 9.94 *d*, *J* = 8 Hz). The latter was attached to vinylic carbon whose proton (δ 5.70, *dd*, *J* = 8, 3 Hz) was involved in vicinal coupling (*J* = 8 Hz) with the aldehyde proton and a long-range coupling with the 7-H_{eq} (*J* = 3 Hz). The two-proton multiplet due to Δ^1 protons of I remained unchanged in II. However, all other protons including those of the methyl groups occurred at higher fields compared to those of I, obviously due to shielding by loss of aromaticity and the appearance of a C-9 ketone. The ketoaldehyde (II) reacted with 2,4-DNP to furnish two products, the major being characterised as the monophenylhydrazone with α,β-unsaturated ketone remaining intact (ν_{max} 1680 cm^{-1}) and the aldehyde group absent (disappearance of $-CHO$ proton).

The unstable II was transformed into III in an inadvertant delayed work-up of the *m*-CPBA reaction of I (in fact for the preparation of III from I, this was the direct procedure used). III was a γ-lactone (ν_{max} 1790 cm^{-1}) with only a feeble absorption in UV (λ_{max} 239 nm, ε = 4,000). Its PMR spectrum was comparable to that of I rather than with II with all its protons occurring at lower fields since the solvent C_6D_6 no longer induced the previous upfield shifts of protons in the cyclic lactone (III). A prominent signal in the PMR spectrum of III was, however, the one at δ 2.44 (*bs*, 11-H_2) in place of the enone proton that disappeared. The formation of III was similar to the classical butenolide rearrangement of furans[3]. Even though a but-2(3)-enolide was usually reported in literature[4], the product in our case was a but-3(4)-enolide with a stable tetrasubstituted double bond (Scheme 1). The structures I and III were supported by mass fragmentation patterns (Scheme 2 and 3 respectively).

Sterols of Dysidea herbacea

The second compounds from hexane extract, apparently pure (TLC and a sharp m.p. at 148°), was in

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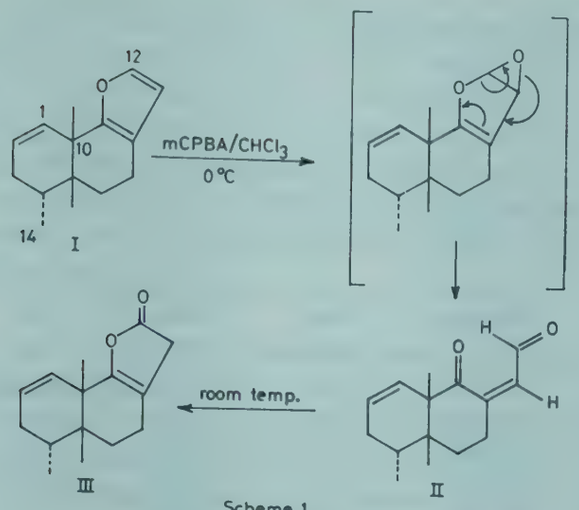
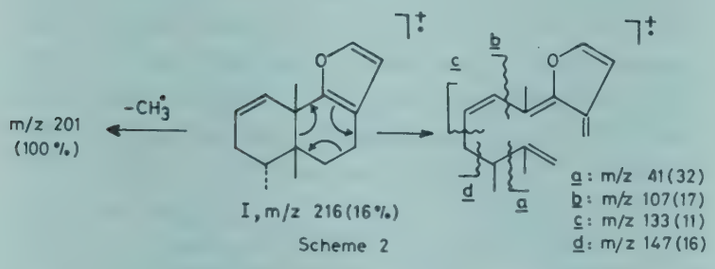
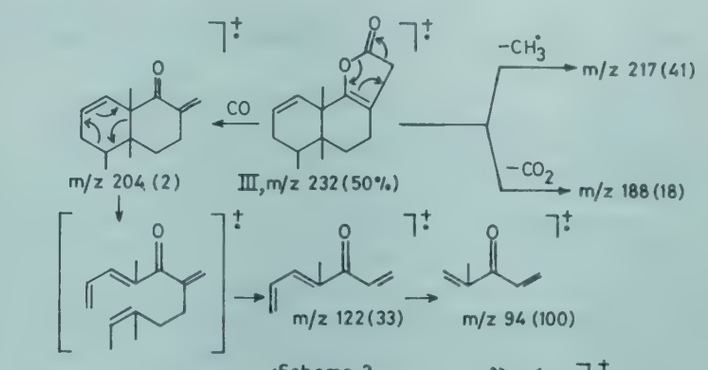


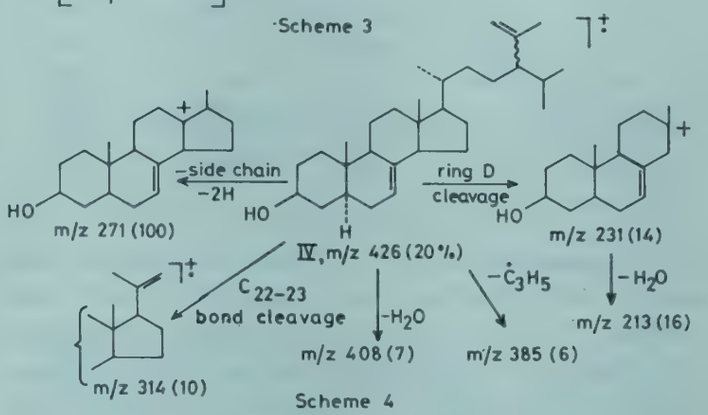
Scheme 1



Scheme 2



Scheme 3



Scheme 4

fact a mixture of three compounds (mixture M) as shown by GC-MS of its acetate which contained peaks at RTs 1.00, 1.98 and 2.17 (relative to cholesteryl acetate, RT, 1.00). However, by PTLC on argentic SiO_2 gel plates, the mixture-M acetate resolved into two bands only. One band (RT, 1.00) was identical with cholesteryl acetate, as revealed by comparison with an authentic sample. The second band which contained the rest of the mixture (compound-B acetate) should have resulted by overlap of two closely similar compounds (corresponding to RTs of 1.98 and 2.17), probably of *R* and *S* epimers as revealed by almost identical mass data.

On hydrolysis, compound-B acetate (IVa) gave the parent alcohol (IV), m.p. 149°. It contained an isopropenyl group [ν_{max} 1640 and 880 cm^{-1} for the olefinic bond; PMR: δ 4.74 (*q*, 1H, *J*= 1 Hz, $-C\langle^{H}_{H}$), 4.61 (*dq*, 1H, *J*= 10.5 Hz, $-C\langle^{H}_{H}$), and 1.54 (*s*, olefinic Me protons)]. A second (trisubstituted) double bond was indicated in the low field region at δ 5.16 (*bs*) besides the five usual Me groups in the high field region. With the ubiquitous 3β-oxy function (δ 3.60 *bm* in IV and 4.65 *bm* in IVa for the 3-H), this additional double bond could not be present at 5,6-positions as otherwise in IV (and IVa), the 6-H should appear at a substantially lower field of δ 5.60 ± 0.10 (ref. 5). Further, the complex pattern of 3α-H suggested a saturated ring-A. At this stage, a Δ^7 as well as $\Delta^{9(11)}$ should be considered and the former was found to account for the 19-Me (0.79*s*) and 18-Me (0.52*s*) resonances by calculations on the basis of Zurcher's rules (Table 1)[6]. The Δ^7 was *inter alia* supported by MS (Scheme 4).

The presence of C-24 isopropenyl moiety in IV received support from the fragments at *m/z* 385 ($M^+ - C_3H_7$, 6%) and 314 ($M^+ - C_8H_{16}$, 10), the latter obtained by allylic cleavage of the C(22)-C(23) bond following the shift of Δ^{28} to the more crowded $\Delta^{24(28)}$. Some sponge sterols were earlier reported to follow a similar fragmentation[7]. The famous McLafferty rearrangement involving Δ^{28} and C(16) should also be expected to produce abundant fragments at *m/z* 384 ($M^+ - 42$) and 328 ($M^+ - 98$) in IV. However, the former fragment was only present feebly (3%) and the latter, totally absent; in Δ^7 sterols, the side-chain extrusion (271, M^+-side chain-2H, 10%) is known to compete with rearrangement by this mechanism[8]. A similar fragmentation was also observed for IVa. This data did not rule out the $C_{11}H_{21}$ side chain of IV (and IVa) to have a Δ^{25}-24-*n*-propyl structure. However, the fact that there were three secondary methyls (PMR) in the side chain, did rule out $C_{11}H_{21}$ side chain. Finally, compound B, established thus as 24ξ-isopropenylcholest-7-en-3β-ol (IV), might be a mixture of *R* and *S* conformers (at C-24). Inseparable mixtures of such epimers are reported in literature[9].

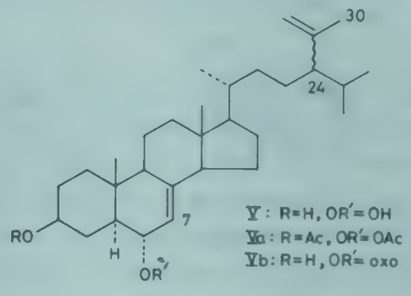
Copmpound C (V), m.p. 198-99°, $C_{30}H_{50}O_2$, purified by PTLC over argentic (10%) silica gel plates (R_f = 0.63, benzeneethyl acetate, 85:15) was found

Table 1 — Calculation of 18-Me & 19-Me Resonances

No.	Group	19-Me				18-Me			
A.	*Common moiety/ group*								
1	5α,14α-androstane	0.792				0.692			
2	Δ^7	−0.008				−0.117			
B.	*Additional groups*	Increment	Value (Calc)	Value (Obsd)	Diff.	Increment	Value (Calc)	Value (Obsd)	Diff.
1	3β-OH (in IV)	+0.033	0.817	0.793	−0.024	+0.008	0.583	0.522	−0.061
2	3β-OAc (in IVa)	+0.050	0.834	0.810	−0.024	+0.008	0.583	0.520	−0.063
3	6α-OH (in V)	−0.008	0.809	0.880	+0.071	+0.008	0.591	0.550	−0.041
4	6α-OAc (in Va)	+0.042	0.876	0.930	+0.054	+0.008	0.591	0.560	−0.031
5	6-Keto (in Vb)	−0.050	0.767	0.860	+0.093	+0.017	0.600	0.590	−0.010

to be homogeneous by GC. The PMR spectra of IV and V (400 MHz) were very similar. The complex pattern of 3α-H_{ax} (3.65, *m*), the signals of isopropenyl group (4.75 *bs* and 4.65 *bs* for $=CH_2$ protons and 1.56 *s* for 30-Me), 19-Me (0.88 *s*), 18-Me (0.55 *s*) and protons of three more methyls at C-21, C-26 and C-27 (1.00-0.84, complex) could all be immediately made out. Even the extra vinylic (trisubstituted) proton (Δ^7) of IV was also recognised in V (5.20, *bs*, $W_{1/2} = 4$ Hz). The only difference between IV and V was that the latter had an extra oxygen in the form of a secondary −OH group (3.80, *bm*, for its geminal 6-H). It gave a diacetate (Va) (2.09 *s* and 2.00 *s* for the protons of the C-6 and C-3 acetoxy groups respectively), in which the protons geminal to acetoxyls underwent down field shift by 1.10 (6-H) and 1.00 ppm (3-H) respectively, relative to those of the diol (V). The extra 6-OH of V was more reactive than 3β-OH to Jones' reagent (in a controlled experiment) suggesting it to be probably allylic. The resulting monoketone (VI) [(λ_{max} 241 nm, $\varepsilon = 14{,}000$)], did not contain the 6-H; besides its 7-H signal was shifted lower field (5.73) as a sharpened singlet. The 6-OH of V could either be α_{eq} or β_{ax}. The latter should, in principle, deshield the 19-Me substantially by 1,3-diaxial interaction which, however, was absent (the deshielding of 19-Me in V was only 0.09 ppm relative to that of IV), i.e. the 6-OH is α_{eq}, a formulation that received support from calculations based on Zurcher's rules (Table 1)[6].

Like in IV (and IVa), the mass spectra of V and Va were dominated by fragments arising by the loss of side chain. However in the mono ketone (VI), the fragment at *m/z* 342 ($M^+ - 98$, 41%) due to McLafferty rearrangement was of equal intensity as compared to that due to side-chain extrusion. Compound C was thus established as 24ξ-isopropenylcholest-7-ene-3β,6α-diol (V) and may have either 24(*R*) or 24(*S*) conformation (single peak in GC).



The isolation of Δ^7 sterols from *Dysidea herbacea* is being reported for the first time, the earlier members in this group of 'unusual' sterols[10] being only the starfish aglycones of *Aesterias amurensis*, all of which have normal side chains[11]. An additional 6α−OH of V is unprecedented so far from not only sponges but marine organisms in general. Looking at the yields of IV (30 mg) and V (260 mg), it might be postulated that the ability of *D. herbacea* to convert an appropriate dietary sterol into a Δ^7-sterol (cf, IV) is almost as much as its efficiency to bio-hydroxylate the allylic C-6 (cf, V). Further, co-occurrence of the potential antifeedant furanosesquiterpene (I) with the sterols (IV) and (V) is noteworthy.

Experimental Procedure

Melting points of all compounds (crystallised from methanol) were determined on VEB. Analytical Dreader HMK hot plate and are uncorrected. Column chromatography was performed on silica gel (100-200 mesh, Acme). The samples were dried at 80°/0.2 mm for 6 hr for analysis and the results were satisfactory. The UV and IR spectra were measured on Shimadzu (double beam and Shimadzu-408 spectrophotometers respectively. The PMR spectra were run on Perkin-Elmer R-32 operating at 90 MHz or JOEL-GX 400 at 400 MHz in $CDCl_3$ (Chemical shifts in δ-scale downfield from TMS internal reference). The GC-MS analyses were carried out on Shimadzu-LKB 9000 (1.5%, OV-17, 275°, N_2 carrier gas) in FID mode.

The *n*-hexane extract of *D. herbacea* (400 g, dry weight after extraction) gave a residue (greenish gum, 22 g) which was chromatographed over silica gel (150 g). Gradient elution[1] gave compound-A (6 g) in fractions (200 ml each) 3-5 (*n*-hexane as eluant), mixture-M (0.03 g) in fractions 90-92 (benzene) and compound-C (0.26 g) in fractions 132-40 (benzene-ethyl acetate, 1:1).

m-Chloroperbenzoic acid oxidation of herbacin (I): Keto-aldehyde (II)

To a well stirred solution of I (0.2 g) in $CHCl_3$ (ice bath, 15 min), *m*-CPBA (0.51 g, 1.5 eq, 80%) in $CHCl_3$ (10 ml) was added dropwise during 20 min. Monitoring by TLC showed only one product (R_f 0.40, benzene). The reaction mixture was immediately washed with 10% aq. $NaHCO_3$, water, dried (Na_2SO_4) and the residue obtained, all in cold conditions. The product II, a light brown gum (yield: 0.17 g, 80%) was purified over silica gel column; IR (film): 2950, 1680, 1670, 1440, 1000, 925 cm^{-1}; PMR (90 MHz, benzene): δ 5.5-5.3 (*m*, 1-H, 2-H), 1.2-1.8 (*m*, 3-H_2, 4-H, 6-H_2, 7-H_2), 0.72 (*s*, 13-Me), 0.47 (*s*, 15-Me), 0.45 (*d*, *J* = 6.5 Hz, 14-Me) (Found: C, 77.5; H, 8.6. $C_{15}H_{20}O_2$ requires: C, 77.6; H, 8.7%).

2,4-*Dinitrophenylhydrazone of II*: m.p. 225° (d), R_f 0.58 (hexane-acetone, 85:15); PMR (90 MHz): 9.05 (*d*, *J* = 2 Hz, 3'-H), 8.4 (*dd*, *J* = 10, 2 Hz, 5'-H), 7.98 (*d*, *J* = 10 Hz, 6-H), 7.86 (*d*, *J* = 10 Hz, 12-H), 6.30 (*d*, *J* = 10 Hz, 11-H), 5.60 (*bs*, $W_{1/2}$ = 6 Hz), 1-H, 2-H), 2.70 (*m*, 7-H_2), 1.80 (*m*, 3-H_2, 4-H, 6-H_2), 1.7 (*s*, 13-Me), 0.95 (*d*, *J* = 6.5 Hz, 14-Me), 0.83 (*s*, 15-Me).

m-CPBA reaction of I: Formation of butenolide (III)

Reaction was performed as described earlier. However, the contents were allowed to stand at room temperature after the addition was over. Monitoring by TLC at intervals showed the gradual disappearance of the original reaction product and corresponding enrichment of a new product (R_f 0.63, benzene). At the end of 6 hr, conversion was complete. The contents were then worked-up as usual afforded a residue (yield: 0.14 g, 70%) which recrystallised from methanol as shining white needles of butenolide (III), m.p. 98°, $[\alpha]_D$ + 36° (*c*, 0.06, $CHCl_3$); IR(KBr): 3010, 1790, 1710, 1240, 1180, 995, 890, 885 cm^{-1}; PMR (CCl_4): 5.52 *dt*, *J* = 10.3 Hz, 2-H), 5.40 (*d*, *J* = 10 Hz, 1-H), 2.95 (*bs*, $W_{1/2}$ = 5 Hz, 11-H_2), 1.97 (*dd*, *J* = 9, 3Hz, 7-H_2), 1.85 (*bs*, $W_{1/2}$ = 8 Hz, 3-H_2), 1.57 (*dd*, *J* = 9, 3 Hz, 6-H_2), 1.13 (*s*, 13-Me), 0.89 (*d*, *J* = 6 Hz, 14-Me), 0.75 (*s*, 15-Me) (Found: C, 77.48; H, 8.6. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.7%).

GC-MS of nixture-M acetate (Ac_2O/Py, room temp., 24 hr):

Cholesteryl acetate (I) (*RT* = 1.00)

MS: *m/z* 428 (M^+, absent), 368 (M^+ − AcOH, 81), 353 (21), 255 (20), 247 (29), 160 (28), 146 (68), 95 (59), 81 (82), 69 (53), 55 (64), 43 (100).

24ξ-*Isopropenylcholest-7-en-3-ol acetate* (*IVa*): MS: *m/z* (RT = 1.98), 468 (M^+, 3), 453 (M^+ − Me, 3), 408 (M^+ − AcOH, 8), 393 (5), 343 (8), 313 (M^+ − side chain-2H, 94), 284 (28), 255 (17), 253 (90), 227 (14), 213 (23), 95 (52), 81 (70), 69 (91), 55 (100), 43 (77).

24ξ-*Isopropenylcholest-7-en-3-ol acetate* (*IVa*) (*RT* = 2.17): MS: *m/z* 468 (M^+, 17), 453 (17), 408 (14), 393 (7), 343 (7), 313 (100), 289 (11), 255 (4), 253 (3), 221 (2), 213 (4), 95 (61), 81 (80), 69 (69), 55 (88), 43 (71).

Purification of mixture-M acetate

Preparative TLC (benzene-ethyl acetate, 95:5) over argentometric (10%) SiO_2 gel plates gave two bands, R_f = 0.83 (identified as cholesteryl acetate by direct comparison, m.p. 115°) and R_f = 0.75 (compound-B).

Compound B, 24 (*R*+*S*)-*isopropenylcholest-7-en-3β-ol acetate* (*IVa*): m.p. 138-39°; UV: No absorption above 220 nm; IR (KBr): 2900, 1730, 1380, 1360, 1260, 1035, 880 cm^{-1}; PMR: 5.10 (*bs*, $W_{1/2}$ = 9 Hz, 7-H), 4.70 (*bs*, $W_{1/2}$ = 6 Hz, 29-H), 4.58 (*bs*, $W_{1/2}$ = 6 Hz, 29'-H), 4.65 *bm*, 3-H), 1.93 (*s*, −COO*Me*), 1.56 (*s*, 30-Me), 1.02-0.75 (*s*, 21-, 26- & 27-Me's), 0.81 (*s*, 19-Me), 0.52 (*s*, 18-Me) (Found: C, 82.0; H, 11.0. $C_{32}H_{52}O_2$ requires C,82.1: H, 11.1%).

Alkaline hydrolysis of IVa: Formation of 24 (*R*+*S*)-*isopropenylcholest-7-en-3-ol* (*IV*): Compound IVa on hydrolysis with 3% KOH/MeOH for 12 hr at room temperature afforded after work-up IV, m.p. 149°; R_f = 0.46 (benzene-ethyl acetate, 90:10); UV; No absorptioon above 220 nm; IR (KBr): 3400-3300, 2900, 1635, 1380-1360, 1090, 1040, 880 cm^{-1}; PMR (400 MHz): 0.93 (*d*, *J* = 6.5 Hz, 21-Me), 0.91 (*d*, *J* = 6.5 Hz, 26-Me), 0.80 (*d*, *J* = 6 Hz, 27-Me) (Found: C, 84.4; H, 11.8. $C_{30}H_{50}O$ requires C, 84.4; H, 11.8%).

Compound-C, 24ξ-*isopropenylcholest-7-en-3β,6α-diol* (*V*): UV: No absorption above 220 nm; IR (KBr): 3400-3300, 2900, 1640, 1460, 1380-1360, 1040, 880 cm^{-1}; MS (*m/z*, %): 442 (M^+, 1), 424 ($M^+ - H_2O$, 22), 409 (11), 406 ($M^+ - 2H_2O$, 8), 391 (31), 365 (7), 351 (6), 315 (8), 297 (6), 271 (M^+ − side chain-H_2O, 39), 269 (271-2H, 24), 253 (271-H_2O, 35), 222 (11), 211 (ring D cleavage-2H_2O, 24), 199 (28), 185 (19), 171 (34), 159 (26), 145 (31), 143 (36), 105 (34), 95 (45), 81 (60), 69

(73), 55 (100), 43 (66) (Found: C, 81.3; H, 11.4. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%).

Diacetate Va (Ac$_2$O/Py room temp, 24 hr)

Semi-solid, $R_f = 0.75$ (benzene); UV: No absorption above 220 nm; IR($CHCl_3$): 2900, 1730, 1380-1360, 1240, 1035, 880 cm^{-1}; PMR (CCl_4): 5.00 (*bs*, 7-H), 4.65 (*s*, 29-H), 4.80 (*s*, 29′-H), 4.90 (*bm*, 6-H), 4.65 (*bm*, 3-H), 1.56 (*s*, 30-Me), 1.00-0.84 (*c*, 21-, 26- & 27-Me's), 0.95 (*s*, 19-Me), 0.56 (*s*, 18-Me); MS (*m/z*, %): 524 (M^+, absent), 466 ($M^+ - AcOH$, 14), 438 (4), 406 ($M^+ - 2AcOH$, 25), 313 ($M^+ -$ side chain-AcOH, 25), 311 (313-2H, 11), 254 (7), 251 (311-AcOH, 14), 227 (17), 202 (11), 201 (20), 199 (25), 158 (26), 157 (25), 145 (25), 143 (30), 95 (44), 93 (28), 81 (55), 69 (60), 55 (75), 43 (100) (Found: C, 77.5; H, 10.2. $C_{34}H_{54}O_4$ requires C, 77.6; H, 10.3).

Oxidation of V: 24ξ-isopropenylcholest-7-en-3β-ol-6-one (Vb)

Compound V (30 mg) in acetone (10 ml) was treated with Jones' reagent (5 drops) at 0°. After 15 min, the reaction mixture was worked-up as usual to give a single product, yield 20 mg (67%), m.p. 192-93°, $R_f = 0.78$ (benzene-ethyl acetate, 90:10); IR(KBr): 3400-3300, 1665, 1380-1360, 1050, 880 cm^{-1}; PMR: 5.73 (*s*, 7-H), 4.75 (*bs*, $W_{1/2} = 5$ Hz, 29-H), 4.65 (*bs*, $W_{1/2} = 5$ Hz, 29′-H), 3.60 (*bm*, 3-H), 1.56 (*s*, 30-Me), 1.02-0.76 (complex, 21-, 26- & 27-Me's), 0.86 (*s*, 19-Me), 0.59 (*s*, 18-Me); MS (*m/z*, %): 440 (M^+, 65), 425 ($M^+ - Me$, 26), 424 (17), 422 ($M^+ - H_2O$, 10), 412 (5), 406 (10), 399 (16), 396 (16), 342 (McLafferty rearrangement, 41), 312 (31), 287 (M^+-side chain, 41), 285 (287-2H, 66), 269 (30), 261 (100), 243 (26), 175 (30), 169 (30), 147 (32), 120 (44), 104 (54), 95 (66) (Found: C, 81.7; H, 11.0. $C_{30}H_{48}O_2$ requires C, 81.8; H, 11.0).

Note added in proof

It has been suggested (D J Faulkner, personal communication) that in the structure elucidation of herbacin (I), an alternative Δ^3-1α-methyl structure should also have been considered. Comparing the ^1H NMR spectra (90 MHz) of I, II and III in C_6D_6, the olefinic 1-H appeared at δ 5.86, 5.50-5.30 and 5.40 respectively (Experimental and ref. 2) and its deshielding in I (relative to II and III) can be operative via the furan moiety in the case of a nearby Δ^1 (as proposed) and not a distant Δ^3.

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References

1 Sarma N S, Rambabu M, Anjaneyulu A S R & Rao C B S, *Indian J Chem*, **25B** (1986) 1001.
2 Cimino C G, De Stefano S, Guerriero A & Minale L, *Tetrahedron Lett*, (1975) 3723.
3 Eugster C H & Bosshard P, *Helv chim Acta*, **46** (1963) 815.
4 Bosshard P & Eugster C H, in *Advances in heterocyclic chemistry*, Vol. VII, edited by A R Katrizky & A J Boulton (Academic Press, New York) 1966, 457.
5(a) Schoolery J N & Rogers M T, *J Am chem Soc*, **80** (1958) 5121.
(b) Okamoto T & Kawazoa K, *Chem pharm Bull (Tokyo)*, **11** (1963) 643.
6 Von Zurcher R F, *Helv chim Acta*, **46** (1963) 2054.
7 Sjostrand U, Kornprobst J M & Djerassi C, *Steroids*, **38** (1981) 355.
8 Zielinski J, Milkova T, Popov S, Marekov N & Djerassi C, *Steroids*, **39** (1982) 675.
9 Berquist P R, Hofneinz W & Oesterhelt G, *Biochem Syst Ecol*, **8** (1980) 423.
10(a) Schmitz F J, in *Marine natural products, chemical biological perspectives*, Vol. I, edited by P J Scheuer (Academic Press, New York) 1978, 241.
(b) Goad L J, in *Marine natural products, chemical biological perspectives*, Vol. II, edited by P J Scheuer (Academic Press, New York) 1978, 76.
11 Kobayashi M, Tsuru R, Toda K & Mitsuhashi H, *Tetrahedron*, **30** (1974) 2147.

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Chemical Constituents of *Melochia corchorifolia* Linn.†

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In addition to known compounds, friedelin, friedelinol, β-amyrin, vitexin, robinin, tetratriacontanol, ethyl stearate, β-sitosterol, β-sitosterol stearate and β-sitosterol-β-D-glucoside, three new compounds have been isolated from the aerial parts of *Melochia corchorifolia* and characterized as 24-ethyl-2-methyltritetracont-1-ene-3,23-diol, 27-methyloctacosane-1,3-diol and nonacosyl non-4-enoate by physicochemical studies.

Melochia corchorifolia Linn. (Sterculiaceae) is one of the two species of the genus *Melochia* occurring throughout the hotter parts of India. The decoction of this plant has been reported in folk medicines as a cure for abdominal swellings, dysentery[1] and water-snake bites[2]. Earlier studies on this plant have resulted in the isolation of three cyclopeptide alkaloids[3] and three flavonoids[4]. Recently, we have also reported new pyridine[5] and cyclopeptide alkaloids[6] from the aerial parts of this plant. Further chromatographic purification of the various extracts has led to the isolation of thirteen more compounds which have been designated as compounds **1-13**. The structural investigations of these compounds are reported in this paper.

Compound-**3**, m.p. 51°, ν_{max} 1739, 1170 (ester >CO), 1600 (double bond), 715 cm^{-1} (long chain) showed in its PMR spectrum two triplets (J=6 Hz) at δ 4.20 and 2.30 for the methylene protons of $-CH_2-O-CO$ and $-CH_2CO-$, respectively, together with a multiplet at 5.30 for olefinic protons suggesting it to be a long chain unsaturated ester. Absence of 970 cm^{-1} band in its IR spectrum revealed the *cis*-nature of the double bond[7].

Compound-**3** on alkaline hydrolysis furnished an alcohol, m.p. 84°, identified as nonacosanol (m.m.p., co-TLC, MS), and an acid, $[M]^+$ 156, $C_9H_{16}O_2$, identified as non-4-enoic acid by comparison with literature data[8] (MS, PMR). This compound was therefore characterized as nonacosyl non-4-enoate.

Compound-**8**, m.p. 101° showed its IR spectrum bands at 3400, 3340 (OH), 2920, 2850, 1465, 715 (long chain) and1660, 1400, 890 cm^{-1} (>C=CH_2)[9]. It analysed for $C_{46}H_{92}O_2$ (M^+ at *m/z* 676 by EIMS and 677 by CIMS). The ion at *m/z* 661 $[M-Me]^+$ and the ratio between the abundances of $[M-Me]^+$ and $[M]^+$ indicated it to be branched having a Me group as substituent[10]. Another strong ion at *M/z* 647 $[M-Et]^+$, and the ions at *m/z* 409, 367, 309 and 267 suggested the presence of an ethyl group (δ 0.94, *t*) at C-24. One of the OH groups was located at C-3 since significant α-fission ions were observed at *m/z* 635, 605, 71 and 41. These ions also indicated the presence of a terminal isopropenyl group with unsaturation at C-1. Similarly, the second OH group was placed at C-23 as the other set of prominent ions were generated at *m/z* 367, 339, 337 and 309. These fragmentations are depicted in Chart 1. In its PMR spectrum the Me group of the isoprenyl function appeared at δ 1.55 whereas the olefinic protons appeared at 5.35. The downfield shift of the terminal methylene protons was possibly due to the adjacent C-3 OH group[11]. The C-3-C*H*(OH)− signal in turn, was also shifted downfield to δ 4.15 when compared to the C-23-C*H*(OH)− signal (δ 3.62). The other end of the chain was terminated by a methyl group (δ 0.85, *t*).

Treatment of **8** with pyridine-Ac_2O afforded a diacetate, m.p. 67°, ν_{max} 1740, 1240 cm^{-1}, δ 2.14, 2.10. The −C*H*(OH)− protons of the parent

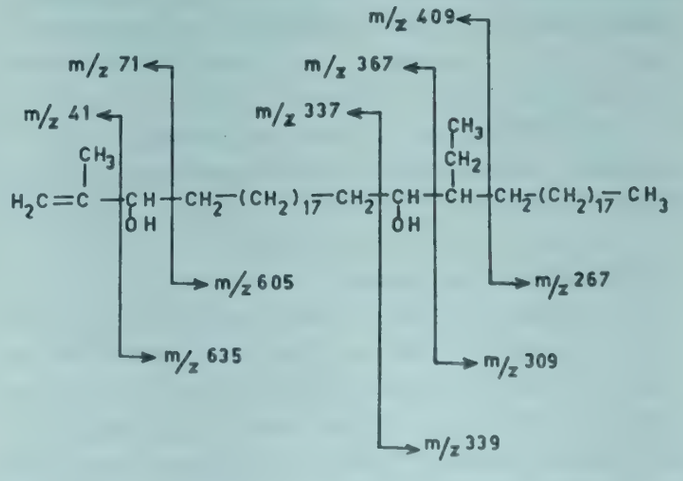

Chart 1—Mass spectral fragmentation pattern of the compound **8**

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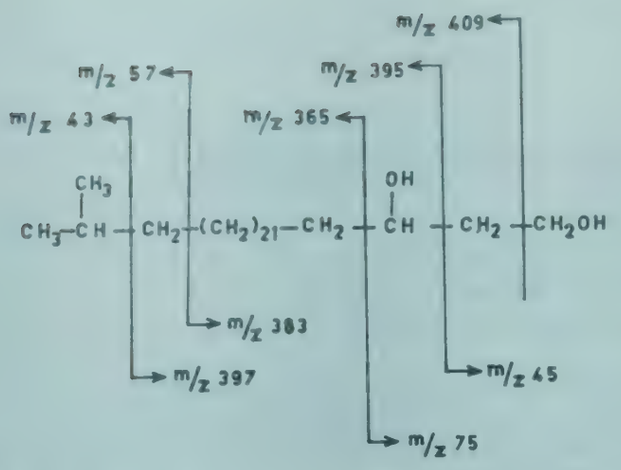

Chart 2—Mass spectral fragmentation pattern of the compound **9**

compound at C-3 (δ 4.15) and C-23 (δ 3.62) were shifted downfield to δ 5.10 and 4.55, respectively. These data were in full accord with the structure of this compound as 24-ethyl-2-methyltritetracont-1-ene-3,23-diol.

Compound-**9**, m.p. 96°, showed ν_{max} 3320 (OH), 2950, 2850, 1465, 712 (long chain), 1380, 1360, 1170 cm^{-1} (isopropyl group)[12]. Its molecular formula as $C_{29}H_{60}O_2$ was obtained from $[M]^+$ at *m/z* 425 together with other ions at *M/z* 397 and 43 suggested the presence of an isopropyl group (δ 0.80, 6H, *d*) at one end of the molecule. The characteristic α-fission ions at *m/z* 395, 365, 75, 45 located one of the OH groups at C-3 while the second OH group was assigned at C-1 due to the appearance of $[M-31]^+$ ion at *m/z* 409 and $[M-H_2O]^+$ ion *m/z* 422. These ions are shown in Chart 2.

Compound-**9**, when treated with pyridine-Ac_2O yielded a diacetate, m.p. 59°, ν_{max} 1732, 1215 cm^{-1}, δ 2.08 and 2.05. The signals for C-1 hydroxymethylene (δ 3.40) and C-3 hydroxymethine (δ 3.60) protons of the parent compound were shifted downfield to δ 3.98 and 5.05, respectively. These data were in full conformity with the structure of this compound as 27-methyloctacosane-1,3-diol.

The identification of the compounds **1**, **2**, **4-7** and **10-13** is described in the experimental procedure.

Experimental Procedure

All melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 399B instrument, UV spectra in MeOH on a Pye-Unicam SP8-100 spectrophotometer, and PMR spectra in $CDCl_3$ on a Varian FT-80A instrument using TMS as internal standard (chemical shift in δ-scale). TLC and preparative TLC were carried out on silica gel G and the spots visualized by exposure to I_2 vapors and ammonia. All the known compounds were identified by preparation of derivatives, spectral data (IR, MS, PMR) and comparison with authentic samples (co-TLC, m.m.p.).

The plant material was collected from Pantnagar, Nainital and identified in our Botany Department where a voucher specimen has been preserved.

Extraction

Dried and powdered aerial part (4.4 kg) of *M. corchorifolia* was extracted with EtOH (7 × 15 l) and the extract concentrated to 350 ml *in vacuo*. The concentrate was added to H_2O (350 ml) and then successively extracted with *n*-BuOH (7 × 1 l each). Removal of solvent yielded hexane extract (91.8 g), $CHCl_3$ extract (10.2 g), BuOH extract (60 g) and these were designated as extracts I, II and III, respectively. Extract II was not worked-up since it was identical with extract I on TLC. Extract III (40 g) was treated with aq. NaOH (2%, 100 ml) and extracted with *n*-BuOH (5 × 100 ml). The solvent was removed *in vacuo* to provide a residue (14.7 g) which was designated as extract IIIa. The basic mother liquor was passed through Amberlite IR 120 resin and the solution extracted with *n*-BuOH (5 × 100 ml). Removal of solvent furnished a residue (21.2 g) which was designated as extract IIIb.

Isolation of compounds from Extract I

A portion of extract I (40 g) was chromatographed over silica gel (1.2 kg, Sisco), eluting with hexane, hexane-C_6H_6 (3:1, 1:1, 1:3), C_6H_6, $C_6H_6-CHCl_3$ (3:1, 1:1, 1:3), $CHCl_3$,$CHCl_3$ – MeOH (99:1, 98:2, 90:10) and MeOH. In all 520 fractions (250 ml each) were collected and monitored by TLC.

*Compound-***1** *(β-sitosterol stearate)*

Removal of solvent from hexane-C_6H_6 (3:1) fractions (25-72) yielded a residue (830 g) which on preparative TLC (100 mg) in hexane-C_6H_6 (1:1) furnished compounds **1** and **2**. Compound-**1** was crystallized from hexane (16 mg), m.p. 88°, $[\alpha]_D$ −26° ($CHCl_3$) and was identified by hydrolysis products, β-sitosterol and stearic acid, m.p. 69°.

*Compound-***2** *(ethyl stearate)*[13]

It was obtained during the preparative TLC of compound-**1** as a viscous mass (35 mg). On alkaline hydrolysis it gave stearic acid.

*Compound-***3** *(nonacosyl non-4-enoate)*

Removal of solvent from hexane-C_6H_6 (3:1) eluates 84-89 furnished a residue which was crystal-

lized from hexane (20 mg), m.p. 51°, R_f 0.76 (C_6H_6); IR: 2920, 2850, 1739, 1600, 1460, 1380, 1170, 715; PMR: 0.85 (6H, *t*, *J*=6 Hz, 2×terminal CH_3), 1.24 [58H, br*s*, $(CH_2)_{29}$], 1.92 (4H, *m*, $-CH_2-CH=CH_2-$), 2.30 (2H, *t*, *J*=8 Hz, $-CH_2-CO-$), 4.20 (2H, *t*, *J*=6 Hz, $-OCO-CH_2-$), 5.30 (2H, *m*, $-CH=CH-$).

Compound-**3** (8 mg) was refluxed with ethanolic KOH (10 ml, 5%) for 5 hr. Its usual work-up afforded nonacosanol, m.p. 84° and non-4-enoic acid (PMR, IR, MS).

*Compounds-***4** *(friedelin) and* **5** *(friedelinol)*

Fractions 97-105 eluted in hexane-C_6H_6 (1:1) were separated by preparative TLC (C_6H_6) into compounds-**4** and **5**. Compound-**4** was crystallized from MeOH (5 mg), m.p. 265°, $[\alpha]_D$ −28° ($CHCl_3$). Compound-**5** was crystallized from MeOH (18 mg), m.p. 300-303°, $[\alpha]_D$ +18°.

*Compound-***6** *(tetratriacontanol)*[14]

Removal of solvent from hexane-C_6H_6 (1:1) eluates (108-32) furnished a residue which was crystallized from acetone (100 mg), m.p. 90°.

*Compound-***7***(β-sitosterol)*

Fractions 153-304 from hexane-C_6H_6 (1:3) and C_6H_6 furnished a residue which was crystallized from methanol (2.5 g), m.p. 133°, $[\alpha]_D$ −34° ($CHCl_3$).

*Compound-***8** *(24-ethyl-2-methyltritetracont-1-ene-3,23-diol)*

Preparative TLC ($CHCl_3$−MeOH, 97:3) of the $CHCl_3$−MeOH (99:1) fractions 457-83 provided a residue which was crystallized from MeOH (15 mg), m.p. 101°, R_f 0.35 ($CHCl_3$−MeOH, 97:3); IR: 3400, 3340, 2920, 2850, 1660, 1465, 1400, 1380, 1090, 890, 715; PMR: 0.85 (3H, *t*, *J*=8 Hz, terminal CH_3), 0.94 (3H, *t*, *J*=8 Hz, CH_3 of C_2H_5 group), 1.55 (3H, *s*, CH_3 at C-2), 1.24 [72H, br*s*, $-(CH_2)_{36}-$], 1.80 (4H, *m*, $-CH_2-$ protons at C-4 and C-22), 1.90 (1H, *m*, methine proton at C-24), 3.62 (1H, *m*, −CH− proton at C-23), 4.15 (1H, *m*, −CH− proton at C-3), 5.35 (2H, *m*, olefinic protons at C-1); MS (rel. int.): *m/z* 676 $[M]^+$ ($C_{46}H_{92}O_2$, 3), 661 $[M-CH_3]^+$ (9), 647 $[M-C_2H_5]^+$ (22), 635 (3), 633 (5), 605 (3), 409 (7), 367 (2), 339 (100), 337 (15), 309 (12), 267 (16), 113 (8), 99(5), 85(12), 71(27), 57(60), 55(38), 43(68), 41(26).

*Acetylation of compound-***8**

Compound-**8** (8 mg) was treated with pyridine-Ac_2O (0.5 ml each) and left overnight at room temperature. Its usual work-up gave a residue which was crystallized from MeOH, m.p. 67°; IR: 2920, 2840, 1740, 1660, 1460, 1400, 1365, 1240, 890, 715; PMR: 0.80 (3H, *t*, *J*=8 Hz, terminal CH_3), 0.90 (3H, *t*, *J*=8 Hz, CH_3 of C_2H_5 group), 1.55 (3H, *s*, olefinic CH_3 group), 1.24 [72H, br*s*, $(CH_2)_{36}$], 1.75 (4H, *m*, $-CH_2$-groups at C-4, C-22), 1.90 (1H, *m*, methine at C-24), 2.10 (3H, *s*, −OAc group at C-23), 2.14 (3H, *s*, −OAc at C-3), 4.55 (1H, *m*, −CH− group at C-23), 5.10 (1H, *m*, methine proton at C-3), 5.35 (2H, *m*, olefinic protons at C-1).

*Compound-***9** *(27-methyloctacosane-1,3-diol)*

Fractions 484-90 from $CHCl_3$−MeOH (98:2) eluates furnished a residue which was crystallized from MeOH (20 mg), m.p. 96°, R_f 0.29 ($CHCl_3$−MeOH, 97:3); IR: 3320, 2920, 2850, 1465, 1380, 1360, 1170, 1120, 1065, 712; PMR: 0.80 [6H, *d*, *J*=8 Hz, $(CH_3)_2CH-$], 1.22 [44H, br*s*, $-(CH_2)_{22}-$], 1.60 (1H, *m*, methine at C-27), 1.80 (4H, *m*, $-CH_2-$ groups at C-2, C-4), 3.40 (2H, *t*, *J*=6 Hz, $-CH_2OH$ at C-1), 3.60 (1H, *m*, −CH− at C-3); MS (rel. int.): *m/z* 440 $[M]^+$ ($C_{29}H_{60}O_2$, 1), 425 $[M-CH_3]^+$ (4), 422 $[M-H_2O]^+$ (2), 409 $[M-CH_2OH]^+$ (1), 407 $[M-CH_3-H_2O]^+$ (2), 397 (20), 395(5), 394(2), 383(5), 369(3), 365(3), 169(2), 155(2), 141(3), 127(5), 113(6), 99(10), 85(36), 75(62), 57(100), 45(5), 43(94).

*Acetylation of compound-***9**

Compound-**9** (10 mg) was acetylated with pyridine-Ac_2O (0.5 ml each) and left overnight at room temperature. When worked-up, it gave a residue which was crystallized from MeOH, m.p. 59°, IR: 2915, 2850, 1732, 1458, 1370, 1360, 1215, 1190, 712; PMR: 0.85 [6H, *d*, *J*=8 Hz, $(CH_3)_2CH-$], 1.24 [44H, br*s*, $(-CH_2)_{22}-$], 1.60 (1H, *m*, −CH− at C-27), 2.05, 2.08 (3H each, *s*, 2×−OAc), 3.98 (2H, *t*, *J*=6 Hz, $-CH_2-OAc$), 5.05 (1H, *m*, −CH−OAc at C-3).

*Compound-***10** *(β-sitosterol-β-D-glucoside)*

Removal of solvent from $CHCl_3$−MeOH (90:10) fractions 503-12, and MeOH washings afforded a residue which on crystallization from MeOH gave compound-**10** (2.9 g), m.p. 278-79°, $[\alpha]_D$ −44° (C_5H_5N). It was identified by its hydrolysis products, β-sitosterol and glucose.

Isolation of compounds from extract IIIa

A portion of extract IIIa (1 g) showing the presence of saponins was hydrolysed with 4*N* HCl (20 ml, 6 hr) and extracted with $CHCl_3$ (5×25 ml).

Removal of $CHCl_3$ yielded a residue (435 mg) and a portion (100 mg) of it was subjected to preparative TLC ($CHCl_3$ – MeOH, 99:1) which afforded β-sitosterol and compound-**11**. The hydrolysate showed the presence of glucose and rhamnose.

Compound-**11** (*β-amyrin*)

It was crystallized from MeOH (8 mg), m.p. 196-97°, $[\alpha]_D$ + 86° ($CHCl_3$).

Isolation of compounds from extract IIIb

A portion of this extract (10 g) was chromatographed over silica gel (400 g) and eluted with varying proportions of $CHCl_3$ and MeOH. A total of 111 fractions (150 ml each) were collected and monitored by TLC.

Compound-**12** (*vitexin*)

Removal of solvent from $CHCl_3$ – MeOH (80:20) fractions 73-80 furnished a yellow residue (630 mg). Preparative paper chromatography (AcOH – H_2O, 15:85) of this residue (20 mg) yielded compound-**12** which gave a yellow powder from EtOH (10 mg), m.p. 261-63° and was identified by UV spectral data and their shift with various reagents.

Compound-**13** (*robinin*)

Fractions 93-104 from $CHCl_3$ – MeOH (1:1) eluates afforded a yellow syrup (1.95 g). Preparative paper chromatography of this syrup (1.95 g). Preparative paper chromatography of this syrup (30 mg) in AcOH – H_2O (15:85) yielded compound-**13** which was crystallized from aq. EtOH (13 mg), m.p. 194-96° and was identified by UV, UV shifts[15], and hydrolysis into kaempherol, galactose and glucose.

Acknowledgement

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References

1 *Wealth of India: Raw Materials*, Vol. 6 (CSIR, New Delhi) 1962, 334.
2 Chopra R N, Nayar S L & Chopra I C, *Glossary of Indian medicinal plants*, (CSIR, New Delhi) 1956, 164.
3 Tschesche R & Reutel I, *Tetrahedron Lett*, (1968) 3817.
4 Nair A G R, Ramesh P, Subramanian S S & Joshi B S, *Indian J Chem*, **15B** (1977) 1045.
5 Bhakuni R S, Shukla Y N & Thakur R S, *Chemy Ind (London)*, (1986) 464.
6 Bhakuni R S, Shukla Y N & Thakur R S, *Phytochemistry*, **26** (1987) 324.
7 Ahmad M S, Rauf A, Mustafa J & Osman S M, *Phytochemistry*, **23** (1984) 2247.
8 Francisco C G, Freire R, Hernandez R, Salazar J A & Suarez E, *Steroids*, **41** (1983) 267.
9 Nakanishi K & Soloman P H, *Infrared Absorption spectroscopy* (Holden-Day, San Francisco) 1977, 17.
10 Stoinova-Ivanova B, Hadjieva P & Popow S, *Phytochemistry*, **8** (1969) 1549.
11 Dabrowski Z, Wrobel J T & Wojtasiewicz K, *Phytochemistry*, **19** (1980) 2464.
12 West W, *Technique of Organic chemistry*, Vol. 9 (Interscience, New York) 1967, 351.
13 Matsuo A, Nakayama M, Hayashi S & Nagai K, *Phytochemistry*, **19** (1980) 1848.
14 Shukla Y N & Thakur R S, *Phytochemistry*, **22** (1983) 973.
15 Mabry T J, Markham K R & Thomas M B, *The systematic identification of flavonoids* (Springer-Verlag, New York) 1970, 121.

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Synthesis of Methyl Glycosides of D-Quinovosamine & D-Fucosamine

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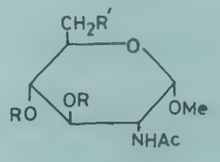
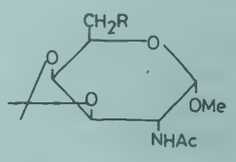
Methyl glycosides of D-quinovosamine (**7**) has been synthesied from D-glucosamine hydrochloride in eight steps. Starting from N-acetyl-D-galactosamine, methyl glycoside of D-fucosamine has been synthesized in six steps. LAH reduction of 6-O-tosyl derivative is found convenient and affords D-quinovosamine and D-fucosamine in reasonably good yields.

Quinovosamine or fucosamine are present in most of the lipopolysaccharides of *Pseudomonas aeruginosa*. While working on the structure and immunochemistry of their O-specific polysaccharides, it was necessary to have fucosamine and quinovosamine and their partially methylated derivatives as reference compounds. D-Quinovosamine has been synthesised recently[1] from N-acetyl-D-glucosamine by reduction of 6-bromo derivative of N-acetyl-D-glucosamine and fucosamine has been prepared[2] by reduction of 6-iodo derivative of N-acetyl-D-galactosamine with Raney nickel catalyst. We find that LAH reduction of the corresponding 6-tosyl derivatives afford D-quinovosamine and D-fucosamine in reasonably good yields.

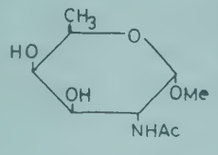
Acetylation (Ac_2O/Py) of D(+)-glucosamine hydrochloride led to the crystalline pentaacetate which on treatment with methanolic hydrogen chloride, afforded methyl 2-acetamido-2-deoxy-α-D-glucopyranoside[3] (**1**). Tritylation[4] of **1** gave crystalline 6-O-trityl derivative (**2**) which on benzylation[5], gave methyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-6-O-trityl-α-D-glucopyranoside (**3**) as fine crystals. Detritylation of **3** followed by tosylation[6] gave methyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-6-O-tosyl-α-D-glucopyranoside (**5**). LAH reduction of **5** under mild condition[7] gave methyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-2,6-dideoxy-α-D-glucopyranoside (**6**) which on further catalytic reduction over Pd/C (10%) gave methyl glycoside of N-acetyl-quinovosamine (**7**). The compound having $[\alpha]_D^{25} + 117.4°$ was characterised by its PMR spectrum, elemental analysis and by GLC analysis as its alditol acetate.

N-Acetyl-D-galactosamine was refluxed with 5 *N* hydrogen chloride in methanol giving a mixture of methyl glycosides[2]. Without separating the component glycosides the mixture was allowed to react with 2,2-dimethoxypropane[8], to give **8** and **8A** together with some unreacted material. PMR spectral study showed that **8** was methyl 2-acetamido-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside and **8A** was methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-α-D-galactofuranoside. Compound (**8**) was tosylated[6] to give a 6-O-tosyl derivative (**9**) which on LAH reduction[7] gave methyl 2-acetamido-2,6-dideoxy-3,4-O-isopropylidene-α D-galactopyranoside (**10**). It was found convenient to use the 3,4-O-isopropylidene derivative (**9**) rather than utilizing the unprotected tosyl compound namely, methyl 2-acetamido-2,6-dideoxy-α-D-galactopyranoside for LAH reduction. Removal of O-isopropylidene group from **10** gave methyl glycoside of N-acetyl-D-fucosamine (**11**). The compound having $[\alpha]_D^{25} + 177°$ was characterised by its PMR spectrum, elemental analyses and GLC.





1	R = H, R′ = OH	8	R = OH
2	R = H, R′ = OTr	9	R = OTs
3	R = Bzl, R′ = OTr	10	R = H
4	R = Bzl, R′ = OH		
5	R = Bzl, R′ = OTs		
6	R = Bzl, R′ = H		
7	R = H, R′ = H		



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Experimental Procedure

General—All reactions were monitored by TLC on silica gel G (Merck). Column chromatography was performed using silica gel 60 (Merck). All solvents were distilled before use and all evaporations were conducted at 50° unless stated otherwise. Optical rotations were measured with a Perkin-Elmer model 241 MC spectropolarimeter. PMR spectra were recorded on a Jeol model FX-100 spectrometer in $CDCl_3$ (internal TMS). GLC of alditol acetates was performed with a Hewlett-Packard model 5730A gas chromatograph, having a flame ionisation detector and a glass column (1.83 m × 6 mm) containing 3% Poly A-103 on Gas Chrom Q (100-120 mesh), at 180°.

Methyl 2-acetamido-2-deoxy-6-O-trityl-α-D-glucopyranoside (**2**)

Compound **1** (8.0 g) was treated with trityl chloride (15 g) in pyridine (60 ml) for 5 days. Excess trityl chloride was destroyed by adding methanol. After 2 hr solvents were evaporated off. The trityl comphy using EtOAC as solvent, yield 62% (10.1 g), m.p. 136-38°; $[\alpha]_D^{24}$ + 33.8° (*c*, 1.4, $CHCl_3$); PMR: δ 1.82 (*s*, 3H, NHAc), 3.2 (*s*, 3H, OCH_3), 7.32 (*m*, 15H, 3 × Ph) (Found: C, 70.6; H, 6.9. $C_{28}H_{31}O_6N$ required C, 70.4; H, 6.5%).

Methyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-6-O-trityl-α-D-glucopyranoside (**3**)

A solution of **2** (5 g) in 1,4-dioxane (40 ml) was mixed with powdered KOH (30 g). Benzyl chloride (20 ml) was added dropwise during 2 hr while the mixture was stirred and heated at 80°. After the addition, heating and stirring were continued for 3 hr more, cooled in an ice-bath, diluted with water, and extracted with dichloromethane (2 × 150 ml). The combined extract was washed with water, dried (Na_2SO_4), filtered, the filtrate evaporated to a syrup, from which benzyl alcohol was removed by azeotropic distillation with water. Column chromatography using 2:1 benzene-ether gave pure **3** (6.3 g; 92%). The compound crystallised from ethanol; m.p. 98-100°; $[\alpha]_D^{24}$ + 57.7 (*c*, 3.52, $CHCl_3$), PMR: δ 1.82 (*s*, 3H, NHAc), 3.2 (*s*, 3H, OCH_3), 7.3 (*m*, 25H, 5 × Ph) (Found: C, 76.4; H, 6.8. $C_{42}H_{43}O_6N$ requires C, 76.7; H, 6.6%).

Methyl 2-acetamido-3,4-di-O-benzyl-2-deoxy-6-O-tosyl-α-D-glucopyranoside (**5**)

Compound **3** (4 g) was detritylated by heating with 80% acetic acid (40 ml) at 90° for 1.5 hr and evaporating the solvent. The hydroxy compound **4** (2.4 g; 94%) had $[\alpha]_D^{24}$ + 101° (*c*, 1.5, $CHCl_3$) and m.p. 178-80°.

Compound **4** (2 g, 4.8 mmol) was tosylated[6] with toluene *p*-sulfonyl chloride (1.38 g, 1.5 mmol) in pyridine (10 ml) for 16 hr. After removing the solvent *in vacuo*, the product (**5**) was purified by column chromatography using EtOAc as an eluent and crystallised from ethanol (2.6 g, 95%), m.p. 130-32°; $[\alpha]_D^{24}$ + 98.7 (*c*, 2.3, $CHCl_3$), PMR: δ 1.80 (*s*, 3H, NHAc), 3.15 (*s*, 3H, OCH_3), 7.25 (*m*, 14H, ring protons of 2 × Ph and one *p*-TsOH) (Found: C, 63.6; H, 6.4. $C_{30}H_{35}O_8NS$ requires C, 63.3; H, 6.2%).

Methyl 2-acetamido-3,4-di-O-benzyl-2,6-dideoxy-α-D-glucopyranoside (**6**)

Compound **5** (1 g) in THF (10 ml) was added dropwise to a suspension of LAH (150 mg) in dry ether (5 ml) and reaction mixture was stirred at room temperature for 1 hr. Excess LAH was destroyed with saturated Na_2SO_4 solution, filtered and the filtrate concentrated. Chloroform (50 ml) was added and the solution was washed with water (5 × 30 ml). The chloroform layer was dried (Na_2SO_4), and evaporated to a syrup. TLC in ethyl acetate gave two spots. The major component was separated by column chromatography using the same solvent, yield 0.42 g (60%); $[\alpha]_D^{24}$ + 88.4° (*c*, 8, $CHCl_3$); PMR: δ 1.25 (*d*, 3H, CH_3, J = 6 Hz), 1.85 (*s*, 3H, NHAc), 3.16 (*s*, 3H, OCH_3), 7.25 (*m*, 10H, 2 × Ph) (Found: C, 70.0; H, 7.1. $C_{23}H_{29}O_5N$ requires C, 69.2; H, 7.3%).

Methyl 2-acetamido-2,6-dideoxy-α-D-glucopyranoside (**7**)

To a solution of **6** (100 g) in ethanol (10 ml) was added 10% Pd/C (80 mg) and stirred under hydrogen for 16 hr at room temperature. The mixture was filtered and the filtrate evaporated to dryness giving 52.2 mg (95%). The residue was purified by column chromatography using ethyl acetate-methanol (19:1) as eluent to afford **7**, yield 46 mg; $[\alpha]_D^{24}$ + 117.4° (*c*, 1.1, methanol). GLC of the material as alditol acetate showed a retention time of 1.57 mm with respect to alditol acetate of glucose (Found: C, 49.2; H, 7.8. $C_9H_{17}O_5N$ requires C, 49.3; H, 7.8%).

Methyl 2-acetamido-2-deoxy-3,4-O-isopropylidene-α-D-galactopyranoside (**8**)

N-Acetyl-D-galactosamine (1 g) was refluxed with 5 *N* hydrogen chloride in methanol (30 ml) for 6 hr. The mixture was neutralised with Ag_2CO_3 and filtered through a Celite bed and the filtrate evaporated to dryness. Without separating the component glycosides the mixture was dissolved in N,N-dimethylformamide and 2,2-dimethoxypropane (25 ml) and *p*-toluene sulfonic acid (50 mg) were added and

the solution was stirred for 16 hr. TLC (ethyl acetate) revealed two spots having R_f values 0.35 and 0.5 respectively together with some unreacted material which remained at the base line. The major component separated by column chromatography with ethyl acetate as solvent was crystallised from ethanol (0.44 g; 35%) to give **8**; $[\alpha]_D^{24} + 178.4°$ (*c*, 1.4, ethanol), m.p. 160-62°. PMR($CDCl_3$): δ 4.70 (*d*, 1H, H-1), 3.35 (*s*, 3H, $-OCH_3$), 2.00 (*s*, 3H, $NHCOCH_3$), 1.55 and 1.32 [2*s*, 6H, $\succ C(CH_3)_2$] (Found: C, 52.5; H, 7.7. $C_{12}H_{21}O_6N$ requires C, 52.4; H, 7.7%).

Methyl 2-*acetamido*-2-*deoxy*-3,4-*O*-*isopropylidene*-6-*O*-*tosyl*-α-D-*galactopyranoside* (**9**)

Compound **8** (0.39) was tosylated as described above and the product crystallised from ethanol to tive **9** (0.4 g, 90%); $[\alpha]_D^{24} + 105.4°$ (*c*, 0.5, $CHCl_3$), m.p. 172°, PMR($CDCl_3$): δ 7.6 (*m*, 4H, 4 ring protons of tosyl), 4.70 (*d*, 1H, H-1), 3.35 (*s*, 3H, $-OCH_3$), 2.44 (*s*, 3H, methyl of tosyl), 2.00 (*s*, 3H, $NHCOCH_3$), 1.55 and 1.32 [2*s*, 6H, $\succ C(CH_3)_2$] (Found: C, 53.5; H, 6.6. $C_{19}H_{27}O_8NS$ requires C, 53.3; H, 6.3%).

Methyl 2-*acetamido*-2,6-*dideoxy*-α-D-*galactopyranoside* (**11**)

Compound **9** (200 mg) in ether (10 ml) was treated with LAH (40 mg) for 2 hr at room temperature as described for **6**. The resulting 2-acetamido-3,4-O-isopropylidene-2,6-dideoxy-α-D-galactopyranoside (**10**) (30 mg; 36%) was isolated by column chroamtography using 1:1 ether-benzene as solvent. Compound (**10**) having $[\alpha]_D^{24} + 124°$ (*c*, 0.6, ethanol) could not be induced to crystallise and was treated directly with 80% acetic acid at 75° for 2 hr. The solvent were removed giving the **11** (20 mg; 78%); $[\alpha]_D^{24} + 177°$ (*c*, 1.1, ethanol) (lit.[2] $[\alpha]_D^{24} + 179°$). GLC of the material as alditol acetate showed a retention time of 1.89 mm compared to the alditol acetate of glucose. The alditol acetate was identical with an authentic sample of fucosamine alditol acetate (Found: C, 49.2; H, 7.8. $C_{19}H_{17}O_5N$ requires C, 49.3; H, 7.8%).

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References

1 Burger P J, Nashed M A & Anderson L, *Carbohydr Res*, **119** (1983) 221.
2 Hurton D, Rodemeyer G & Saeki H, *Carbohydr Res*, **59**(1977) 607.
3 Fujinaga M & Matsushima Y, *Bull chem Soc Japan*, **37** (1964) 468.
4 Roy N & Rao A S, *Carbohydr Res*, **59** (1977) 393.
5 Glaudemans C P J & Fletcher (Jr) H G, *J Am chem Soc*, **87** (1965) 4636.
6 Perry M B & Daoust V, *Can J Chem*, **52** (1974) 3251.
7 Gigg J, Gigg R, Payne S & Conant R, *Carbohydr Res*, **141** (1985) 91.
8 Ueno Y, Hori K, Kiso M, Hasegawa A & Kato K, *Carbohydr Res*, **89** (1981) 271.
9 Roy N & Rao A S, *Indian J Chem*, **19B** (1980) 161.

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Quantitative Structure-Activity Relationships: Part IX— A Modified Connectivity Index as Structure Quantifier

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A modified connectivity index, called perturbation connectivity index and represented by $^{m}\chi_t^{p^v}$, is defined as a topological structure descriptor for quantitative structure-activity relationship (QSAR) studies. The modification is introduced at the stage of assigning δ-values to the vertices of a hydrogen suppressed graph (HSG). The newly defined perturbation δ-values (δ^{p^v}) incorporate effects of atomic environments at topological level in terms of a parameter γ_{ij} which measures perturbation induced by an atom j connected to atom i. For zero value of all γ_{ij} terms our approach reduces to Kier's approach of valence connectivity indices. Correlations are obtained between perturbation connectivity indices and anaesthetic activity and toxicity of a set of 13 *n*-alkanes. The results are compared with those obtained using the corresponding $^{m}\chi_t^{v}$ parameters.

Connectivity indices[1] are unitless topological structure quantifiers. A variety of physicochemical[1-8] and biological properties[1,2,9-18] of compounds have been shown to be significantly correlated with connectivity indices of different orders and types.

The computation of connectivity indices associated with a molecule begins with the assignment of numerical values, called δ-values, to every node of the hydrogen suppressed graph (HSG) which represents topology of the non-hydrogen atoms of the molecule. Initially no distinction was considered for single and multiple bonds and all the non-hydrogen atoms of a molecule were topographically treated at par. In that case the δ-value assigned to a vertex represents the connectivity δ-value (δ^c) which is the number of edges converging at that vertex. The specific treatment of heteroatoms, charged atoms and multiple bonds was later attempted[19] by assignment of valence δ-values (δ^v). The δ^v-values, for first row atoms, are defined by Eq. (1) and for higher heteroatoms Eq. (2) is employed to calculate δ^v-values.

$$\delta_i^v = z_i^v - h_i \qquad \ldots (1)$$

$$\delta_i^v = \frac{z_i^v - h_i}{z_i - z_i^v} \qquad \ldots (2)$$

The halogens were assigned empirical δ^v-values[19] to begin with, but recently[2] a common general expression (Eq. (3)) has

$$\delta_i^v = \frac{z_i^v - h_i}{z_i - z_i^v - 1} \qquad \ldots (3)$$

been given for calculation of δ^v-values for all the heteroatoms.

Neither of the schemes, employing δ^c or δ^v, however, accounts for different environments of an atom in a molecule. For instance, in HSG of methyl isobutanoate (Fig. 1) the δ^v-values assigned to methyl carbon 1 (or 6) of the isopropyl group and the methyl carbon of the ester moiety are the same in spite of their different topochromatic environments. Same is true about the two oxygens. In this paper we propose a scheme to define δ-values which carry the effects of different atomic environments. The newly defined δ-values

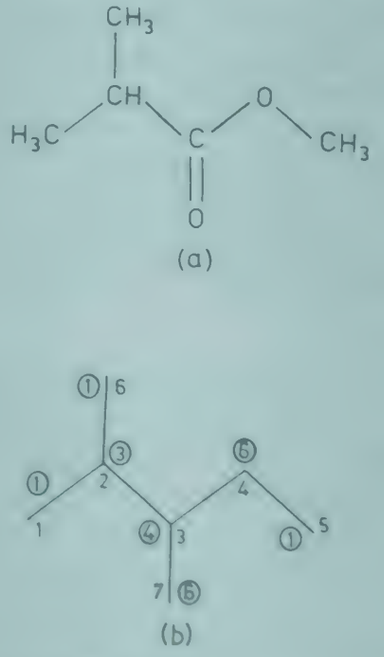

Fig. 1 – Structure (a), HSG (b), numbering and δ^v-values (encircled) of methyl iso-butanoate.

were named perturbation δ-values and represented by $\delta^{p(v)}$. Using these $\delta^{p(v)}$-values we calculated the modified connectivity indices, called perturbation connectivity indices ${}^{m}\chi_t^{p(v)}$. In the first instance the quantitative correlations between these modified connectivity indices and (i) anaesthetic activity and (ii) toxicity of a set of 13 *n*-alkanes on mice were investigated. The statistical quality of the relationships obtained was compared with that computed using valence connectivity indices and other topological parameters.

Theory

In an HSB of *n*- vertices the perturbation δ-value ($\delta^{p(v)}$) for the i-th vertex is related to δ^{v} value according to Eq. (4)

$$\delta_i^{p(v)} = \delta_i^{v} + \sum_{j=1}^{n_c} \gamma_{ij}\, \delta_j^{p(v)} \qquad \ldots (4)$$

where n_c is the number of vertices connected to the i-th vertex. γ_{ij} is the parameter representing perturbation induced, in δ^{v} value of atom i, by atom j connected to it. The set of n $\delta^{p(v)}$-values is, therefore, calculable by solution of Eq. (5).

$$\chi \Delta^{p(v)} = \Delta^{v} \qquad \ldots (5)$$

Here χ is a square matrix whose elements are:

$x_{ij} = 1$;

$x_{ij} = 0$ when vertices i and j are not connected;

and

$x_{ij} = -\gamma_{ij}$ for all vertices i and j sharing an edge.

The column vectors $\Delta^{p(v)}$ and Δ^{v} are of the order n and their elements are $\delta_i^{p(v)}$ and δ_i^{v}, respectively.

For the solution of Eq. (5) it is essential that the numerical values of perturbation parameters (γ_{ij}) are known. Ideally these would be a function of the properties of the connected atoms i and j. However, in the HSG of an *n*-alkane all but the terminal C−C connections are identical. Consequently, for the present work we have assumed all the perturbation terms to be equal ($\gamma_{ij} = \gamma_{ji} = \gamma$) and treated them as empirical parameters. The γ value was varied from −0.30 to +0.30 with an increment of 0.05.

It is obvious that for $\gamma = 0$, the $\delta^{p(v)}$ values are the same as δ^{v} values and, hence, ${}^{m}\chi_t^{p(v)}$ and ${}^{m}\chi_t^{v}$ values are identical. The approach of Kier and Hall[19] can therefore be considered as a special case of our general approach. It can be further seen that when the right hand side of Eq. (5) is replaced by a column vector containing the number of valence electrons for each vertex, the $\delta^{p(v)}$-values become identical with the δ-values used by Commarata[20] to define branching indices M′ and A′. As a matter of fact perturbation can be incorporated to any set of δ-values[5].

After the δ-values are calculated, the modified perturbation connectivity indices of the order m and type t, ${}^{m}\chi_t^{p(v)}$, are computed in a usual manner[1]. All the subgraphs (${}^{m}g_t$) of the order m and type t are identified and contribution C_i (Eq. 6).

$$C_i = \prod_{k=1}^{m+1} (\delta_k^{p(v)})_i^{-\frac{1}{2}} \qquad \ldots (6)$$

of each subgraph is computed and added to obtain the required connectivity index.

Materials and Methods

An interactive software package TOPCOR containing routines for calculation of (i) pertrbation δ-values for any chosen value of γ and (ii) connectivity indices from zero to seventh order of various types was developed and used for this work. This package also contained a routine for stepwise regression analysis. All computations were carried out on a DEC-2050 machine at the Regional Computer Centre, Chandigarh.

As an initial test on the usefulness of the newly defined perturbation connectivity indices in QSAR studies we selected to correlate them with (i) anaesthetic activity, (AD_{100}) for the loss of righting reflex of mice by a set of 13 *n*-alkanes and (ii) toxicity (LD_{100}) of the same set of alkanes to mice after intravenous administration. Anaesthetic activity converted[22] to log ($1/AD_{100}$) and toxicity values converted to log ($1/LD_{100}$) were used as dependent variables in regression analysis. The connectivity indices calculated for all values of γ varying from −0.30 to +0.30 by a stepwise increment of 0.05 constituted the set of independent variables. Keeping in mind the limited size of the set, only one variable and two-variables correlations were attempted.

Results and Discussion

Anaesthetic activity

Among all the 1-variable and 2-variable correlations tried, a 2-variable correlation in ${}^{1}\chi^{p(v)}$ and ${}^{2}\chi^{p(v)}$ (Eq. 7) resulted in the best statistics for −0.20 value of γ†.

$$-\log AD_{100} = 149.3 - 522.1\ {}^{1}\chi^{p(v)} + 954.1\ {}^{2}\chi^{p(v)}$$

$$(n = 13;\ r = 0.996;\ s = 0.042;\ F_{2,10} = 614) \qquad \ldots (7)$$

†For other γ values poorer correlations were obtained. For γ = 0.10, −0.05 and −0.15. For instance, the correlation coefficients were 0.762, 0.775 and 0.853 respectively.

Using the corresponding valence connectivity indices, Eq. (8)

$$-\log AD_{100} = 0.130 + 0.219\ {}^{1}\chi^{v} - 0.094\ {}^{2}\chi^{v}$$

$$(n = 13;\ r = 0.722;\ s = 0.322;\ F_{2,10} = 5.5) \qquad \ldots (8)$$

was obtained which gave a standard error of 0.322 which is much larger than the experimental standard error[22] of 0.17 calculated from the confidence limits at $p = 0.05$ for the experimental data. Eq. (7) is significant at $p < 0.01 < F_{2,10,0.01} = 99$) and explains 99% variance in anaesthetic activity.

Ray *et al.*[23] have obtained a parabolic correlation of comparable quality using information theoretic parameter, structural information content (SIC).

Toxicity

For toxicity of the same set of *n*-alkanes the valence connectivity indices again yielded much poorer correlation (Eq. 9)

$$-\log LD_{100} = 0.484\ {}^{1}\chi^{v} - 0.500\ {}^{2}\chi^{v} + 0.262$$

$$(n = 13;\ r = 0.698;\ s = 0.30;\ F_{2,10} = 4.7) \qquad \ldots (9)$$

than that obtained using first and second order perturbation connectivity indices with $\gamma = -0.22$. Eq. (10).

$$-\log LD_{100} = -276.6\ {}^{1}\chi^{p(v)} + 523.6\ {}^{2}\chi^{p(v)} + 73.1$$

$$(n = 13;\ r = 0.969;\ s = 0.10;\ F_{2,10} = 77.6) \qquad \ldots (10)$$

is significant at $p < 0.025 < F_{2,10,0.025} = 39$) and explains about 95% variance in toxicity data.

Conclusion

On the basis of the above data it has been concluded that the newly defined perturbation connectivity indices carry better structure quantification than the corresponding ${}^{m}\chi^{v}$ indices. The difference in the value of γ for different properties indicates the difference in the perturbation effects of neighbouring atoms in case of different properties. For series other than *n*-alkanes, the γ_{ij} values may have to be taken according to the topography and topochromaticity of the bonded atoms i and j. Such studies are in progress.

References

1 Kier L B & Hall L H, *Molecular connectivity in chemistry and drug research* (Academic Press, New York) 1976.
2 Kier L B, in *Physical chemical properties of drugs*, edited by S H Yalkowsky, A A Sinkula & S C Valvani (Marcel Dekker, New York) 1980.
3 Gombar V, Kapoor V K & Jain D V S, *Indian J Chem*, **19A** (1980) 715.
4 Boyd J C, Millership J S & Woolfson A D, *J Pharm Pharmacol*, **34** (1982) 362.
5 Jain D V S, Singh S & Gombar V, *Proc Indian Acad Sci (Chem, Sci)*, **93** (1984) 927.
6 Jain D V S & Gombar V, *J chem Soc Faraday Trans-I*, **75** (1979) 1132.
7 Sabljic A & Protic M, *Bull Environm Contam Toxicol*, **28** (1982) 162.
8 Sabljic A, *J Agric Food Chem*, **32** (1984) 243.
9 Kier L B & Hall L H, *Eur J mednl Chem-Chiemica Therapeutica*, **12** (1977) 307.
10 Basak S C, Gieschen D P, Magnuson V R & Harries D K, *IRCS Medical Science*, **10** (1982) 619.
11 Kier L B, Hall L H, Murray W J & Randic M, *J pharm Sci*, **64** (1975) 1971.
12 Kier L B & Hall L H, *Eur J mednl Chem-Chemica Therapeutica*, **16** (1981) 399.
13 Boyd J C, Millership J S & Woolfson A D, *J Pharm Pharmacol*, **34** (1982) 158.
14 Kier L B, Murray W J & Hall L H, *J mednl Chem*, **18** (1975) 1272.
15 Murray W J, Kier L B & Hall L H, *J mednl Chem*, **19** (1976) 573.
16 Kier L B & Hall L H, *J mednl Chem*, **20** (1977) 1631.
17 Sabljic A & Protic M, *Chem-biol Interactions*, **42** (1982) 301.
18 Gupta S P, Singh P & Bindal M C, *Chem Rev*, **83** (1983) 633.
19 Kier L B & Hall L H, *J pharm Sci*, **65** (1976) 1806.
20 Cammarata A, *J pharm Sci*, **68** (1979) 839.
21 Jeppsson R, *Acta Pharmacol Toxicol*, **37** (1975) 56.
22 DiPaolo T, *J pharm Sci*, **67** (1978) 566.
23 Ray S K, Basak S C, Roychaudhury C, Roy A B & Ghosh J J, *Indian J Pharmacol*, **13** (1981) 301.

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Notes

Photolysis of 1,2-Naphthoquinone-1-methide Dimers

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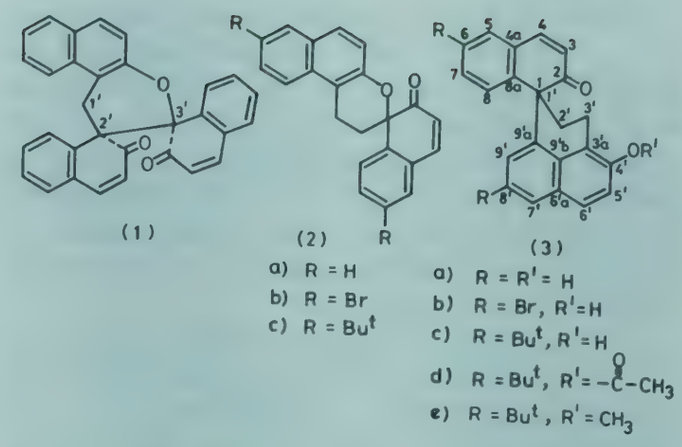
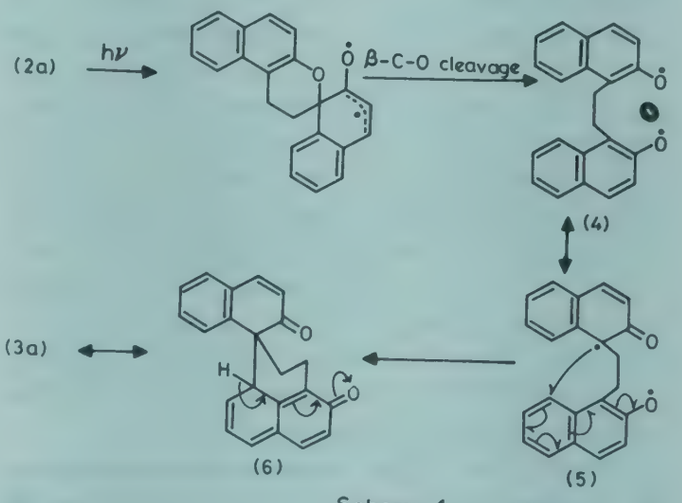
1, 2-Naphthoquinone-1-methide dimer (**2a**) on photolysis isomerises to the phenolic phenalene derivative (**3a**) via a β—C—O cleavage. Similar results are obtained with the dimers (**2b**) and (**2c**)

An X-ray crystallographic investigation[1] of *cis*-dispironaphthalenone (**1**) showed that the $C_{2'}$—$C_{3'}$ bond was unusually stretched (1.616 A°). A wide range of products resulting from β-cleavages and intramolecular cycloaddition were isolated in the photolysis[2] of **1**. Although, the driving force for the β—C—C cleavage was considered to be due to the weakness of $C_{2'}$—$C_{3'}$ bond, the β—C—O bond, which did not exhibit any unusual characteristics in the X-ray crystal structure analysis, also underwent cleavage during photolysis. Hence, the major driving force for the β-cleavages in **1** was attributed to the stability of resultant diradical. In this context, it was considered that the 1, 2-naphthoquinone-1-methide dimer **(2a)** might also exhibit similar β—C—O cleavage on photolysis. With this in view, the photolysis of dimers (2**a—c**) was studied.

The UV spectrum of displays absorption maxima (C_2H_5OH) at 247 (ε21,840), 268(5,980), 277 (8,320), 288(9,879), 312(10,920) and 324 nm (5,980), very similar to those of **1**. When a 0.01 *M* solution of **2a** in benzene was irradiated, no change was observed in its UV spectrum even after 30 hr. However, when a solution of **2a** in methanol (0.005 *M*) was irradiated, the yellow solution became almost colourless in about 16 hr. Methanol was completely removed *in vacuo* and the residue was found to contain (TLC) mainly a highly polar compound. The major product was separated by preparative TLC and further purified by crystallisation. The IR (nujol) spectrum of this compound [*m/z* 312 (M^+)] exhibited a broad bond in the region 3300-3100 cm^{-1} attributable to νOH, in addition to a bond at 1635 cm^{-1} (conjugated CO). From a detailed study of its PMR and CMR spectral data, this compound was identified as the phenolic phenalene derivative (**3a**), which was earlier reported to be formed by heating **2a** in hydrocarbon solvents[3], acetic acid[3], dimethyl sulphoxide[4], or trifluorocetic acid[4].





Scheme 1

We believe that the formation of **3a** occurs via mechanism shown in Scheme 1. An analogous mechanism has been proposed earlier for the thermal isomerisation of **2a** in hydrocarbon solvents[3].

Similarly, photolysis of **2b** and **2c** resulted in the corresponding phenalene derivatives (**3b**) and (**3c**) and these were characterised by their physical data. It may be pointed out here that while the PMR spectrum of **3b** was similar to that of **2b**, that of **3c** exhibited two multiplets in the high field region (δ0.82-0.93 and 1.46-1.75), in addition to the expected signals. Satisfactory analytical data could not be obtained as it kept on varying on repeated purification by crystallisation from chloroform-petroleum ether. However, the mass spectrum of **3c** exhibited the expected molecular ion at m/z 424 (M^+) and also fragment ions at *m/z* 407 $(M—OH)^+$ and 396 $(M—CO)^+$, similar to those seen in **3a** and **3b**. In addition, fragments at *m/z* 367 $(M—C_4H_9)^+$ and 57 $(C_4H_9)^+$ were also seen. In view of this discrepancy, the corresponding acetate (**3d**) and methyl ether (**3e**) were prepared. These compounds exhibited the expected PMR signals and also

gave the correct elemental analyses†. Hence, the structure (**3c**) is beyond doubt. However, it is not very clear how the extraneous signals arise‡ in the PMR spectrum of **3c**.

All irradiations were carried out using immersion-type 450 W medium pressure mercury lamp with water cooled pyrex immersion-well, after bubbling nitrogen through the solution for 1 hr. In all cases, the solvents were completely removed *in vacuo* and the products, isolated by preparative TLC (silica gel, 23:2 chloroform-ethyl acetate), were further purified by recrystallisation. Petroleum ether refers to the fraction boiling in the range 60-80°.

(a) Irradiation of quinonemethide dimer (2a)[1] (250 mg) in methanol (160 ml) for 16 hr gave 2′, 3′-dihydro-4′-hydroxy-spiro {naphthalene-1(2*H*), 1′-[1*H*]phenalen}-2-one (**3a**) (140 mg), m.p. 239-41° (acetone-pet ether) (lit.[3] m.p. 239-41° and lit.[4] m.p. 242°); MS: *m/z* 312(M^+), 295 $(M-OH)^+$ and 284 $(M-CO)^+$; UV ($CHCl_3$): 245 (ε17,561), 287 (11,232), 297 (14,709) and 308 nm (11,945); CMR§ (DMSO-d_6): 18.35 (*t*, C-2′), 35.74 (*t*, C-3′), 57.13 (*s*, C-1 or 1′), 115.39 (*s*, C-3′a), 117. 56 (*d*, C-5′), 121.87 (*d*, C-9′), 123.42 (*d*, C-8), 126.11 (*d*, C-3), 126.71 (*d*, C-7′), 126.95 (*d*, C-6′), 126.95 (*d*, C-8′), 127.78 (*s*, C-6′a), 128.78 (*d*, C-6), 129.68 (*d*, C-5), 129.68 (*d*, C-7), 129.78 (*s*, C-4a), 132.10 (*s*, C-9′a), 134.85 (*s*, C-9′b), 144.74 (*d*, C-4), 146.94 (*d*, C-8a), 150.58 (*s*, C-4′)) and 201.85)*s*, C-2) (Found: C, 84.9; H, 5.4. $C_{22}H_{16}O_2$ requires C, 84.6; H, 5.1%).

(b) Irradiation of dibromoquinonemethide dimer (**2b**)[1] (200 mg) in methanol (175 ml) for 22 hr gave **3b** (100 mg), m.p. 272-73° (ethyl acetate-petroleum ether); MS: *m/z* 468 (M^+), 451 $(M-OH)^+$ and 440 $(M-CO)^+$; UV($CHCl_3$): 249 (ε31,920), 286(15,000), 300 (16,680) and 350 nm (3,960); IR (nujol): 3400-3200 and 1645 cm^{-1}; PMR (DMSO-d_6): 2.09 (2H, *t*, *J*= 5.6 & 6.9 Hz, H_2-2′), 2.72-2.90 (2H, *m*, H_2-3′), 6.24 (1H, *d*, *J*= 9.9 Hz, H-3), 6.72 (1H, *d*, *J*= 8.4 Hz), 6.75 (1H, *d*, *J*= 2.0 Hz), 7.27 (1H, *d*, *J*= 8.8 Hz), 7.51 (1H, *dd*, *J*= 8.4 & 2.2 Hz), 7.72 (1H, *d*, *J*= 8.8 Hz), 7.81 (1H, *d*, *J*= 9.9 Hz, H-4), 7.89 (1H, *d*, *J*= 2.2 Hz), 8.00 (1H, *d*, *J*= 2.0 Hz) and 9.89 (1H, *s*, OH) (Found: C, 56.1); H, 3.0. $C_{22}H_{14}O_2Br_2$ requires C, 56.2; H, 3.0%).

(c) Irradiation of di-*t*-butylquinonemethide dimer (**2c**)[1] (210 mg) in methanol (200 ml) for 24 hr gave **3c** (145 mg), m.p. 160-62° (chloroform-pet. ether); UV ($CHCl_3$): 245 (ε 26,261), 282 (1,215), 295 (13,951) and 308 nm (12,720); IR ($CHCl_3$): 3460-3240 and 1645 cm^{-1}; PMR ($CDCl_3$): 0.82-0.93 (*m*), 1.25 (9H, *s*, Bu^t), 1.34 (H, *s*, Bu^t), 1.46-1.75 (*m*), 2.12-2.32 (2H, *m*, H_2-2′), 2.83-3.03 (2H, *m*, H_2-3′), 5.03 (1H, *s*, OH), 6.23 (1H, *d*, *J*= 9.8 Hz, H-3), 6.76 (1H, *d*, *J*= 8.3 Hz), 6.96 (1H, *d*, *J*= 1.9 Hz), 7.06 (1H, *d*, *J*= 8.8 Hz), 7.22 (1H, *dd*, *J*= 8.3 & 2.1 Hz), 7.40 (1H, *d*, *J*= 2.1 Hz), 7.57 (1H, *d*, *J*= 9.8 Hz, H-4), 7.645 (1H, *d*, *J*= 8.8 Hz) and 7.648 (1H, d, *J*= 1.9 Hz).

Acetylation of **3c** with acetic anhydride-pyridine gave the acetate (**3d**), m.p. 88-90°; MS: *m/z* 466 (M^+); IR (nujol): 1760 and 1665 cm^{-1}; PMR ($CDCl_3$): 1.26 (9H, s, Bu^t), 1.34 (9H, *s*, Bu^t), 2.08-2.38 (5H, *m*, H_2-2′ & $-OCCH_3$), 2.76-3.03 (2H, *m*, H_2-3′), 6.22 (1H, *d*, *J*= 9.9 Hz, H-3), 6.73 (1H, *d*, *J*= 8.2 Hz), 7.01 (1H, *d*, *J*= 2.0 Hz), 7.19-7.25 (2H, *m*), 7.40 (1H, *d*, *J*= 2.0 Hz), 7.56 (1H, *d*, *J*= 9.9 Hz, H-4), 7.73 (1H, *d*, *J*= 2.0 Hz) and 7.77 (1H, *d*, *J*= 8.9 Hz) (Found: C, 82.0; H, 7.3. $C_{32}H_{34}O_3$ requires C, 82.4; H, 7.4%).

Methylation of **3c** with dimethyl sulphate and potassium carbonate in acetone afforded the methyl ether (**3e**), m.p. 124-25° (Petroleum ether); MS: *m/z* 438 (M^+); IR ($CHCl_3$): 1660 cm^{-1}; PMR ($CDCl_3$): 1.26 (9H, *s*, Bu^t), 1.33 (9H, *s*, Bu^t), 2.10-2.29 (2H, *m*, H_2-2′), 2.90-3.09 (2H, *m*, H_2-3′), 3.95 (3H, *s*, OCh_3), 6.22 (1H, *d*, *J*= 9.9 Hz, H-3), 6.74 (1H, *d*, *J*= 8.3 Hz), 6.97 (1H, *d*, *J*= 2.0 Hz), 7.19 (1H, *dd*, *J*= 8.3 & 2.1 Hz), 7.28 (1H, *d*, *J*= 8.9 Hz), 7.39 (1H, d, *J*= 2.1 Hz), 7.55 (1H, *d*, *J*= 9.9 Hz, H-4), 7.66 (1H, *d*, *J*= 2.0 Hz) and 7.76 (1H, *d*, *J*= 8.9 Hz) (Found: C, 84.4; H, 7.8. $C_{31}H_{34}O_2$ requires C, 84.9; H, 7.8%).

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† Hydrolysis of the acetate (**3d**) gave a hydroxy compound (crystallised from chloroform-pet ether), which exhibited the same additional signals in its PMR spectrum as **3c**

‡ The possible existence of conformational isomers due to hydrogen bonding was ruled out by an inspection of its molecular models.

§ Carbon-13 assignments are based on the detailed study of CMR spectra of related spironaphthalenones[1].

References

1 Kasturi T R, Rajashekhar B, Raju G J, Madhusudhan Reddy G, Sivaramakrishnan R, Ramasubbu N & Venkatesan K, *J chem Soc, Perkin Trans.* **1** (1984) 2375.

2 Kasturi T R, Raju G J & Ramamurthy V, *Chem Commun.* (1981) 557.

3 Catterall G, *Chem Commun.* (1974) 41.

4 Dick A W S, Dean F M, Matkin D A & Robinson M L, *J chem Soc, Perkin Trans.* **1** (1977) 2204.

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Photodimerisation of Aryl β-(2-Furyl)-vinyl Ketones†

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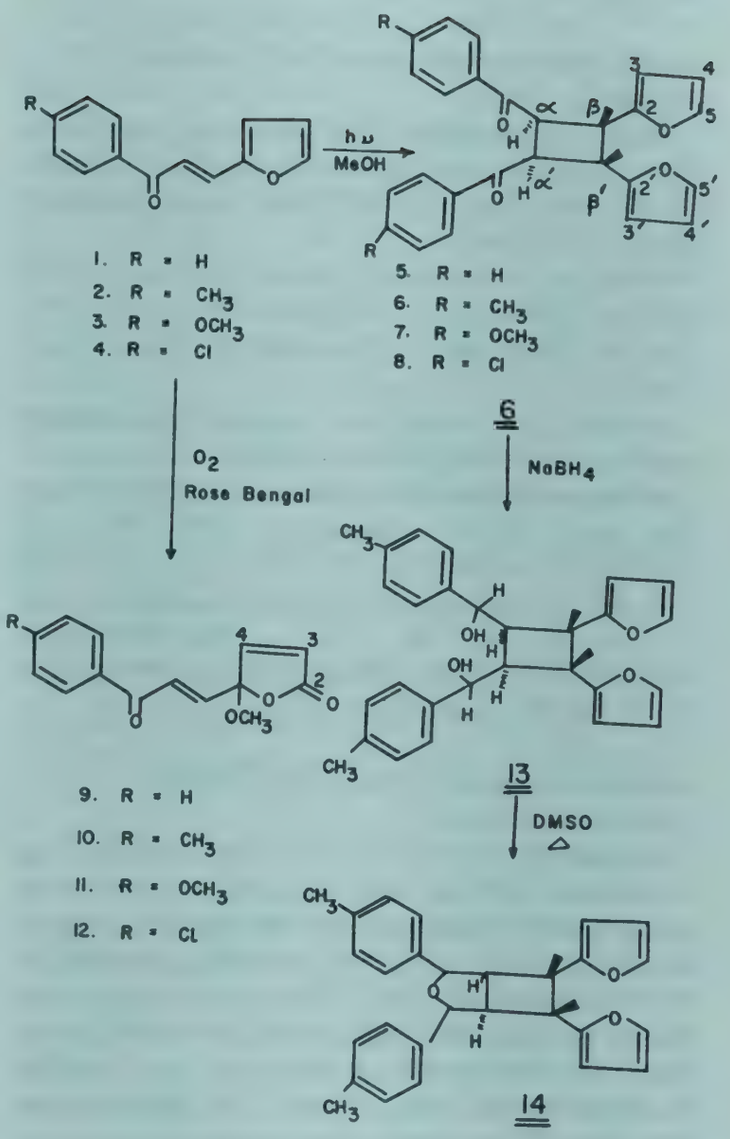
Aryl *β*-(2-furyl)vinyl ketones (**1-4**) on photoirradiation gave the corresponding dimers (**5-8**) having *cis-anti-cis* configuration. The stereochemistry of these dimers has been established by reduction of **6** to diol **13**, which on subsequent dehydration gave the ether **14**. Whereas dye-sensitized photooxidation of **1-4** in the presence of rose bengal affords the corresponding lactones **9-12**. The structures of these photoproducts have been established on the basis of their PMR and mass spectral data.

Aryl β(2-furyl)vinyl ketones are known to undergo an interesting acid catalysed rearrangement to 5-arylfuran-2-propionic acid[1]. A mechanism for this reaction was proposed by Short and Rockwood[2] and the generality of this reaction established with quinolyl, pyridyl and other *p*-nitrophenyl derivatives[3]. Further it was shown that when refluxed with ethanolic hydrochloric acid, these compounds give the propionic esters directly[4]. In an attempt to see whether aryl β-furylvinyl ketones undergo rearrangement analoguous to the above type, several such ketones were subjected to photoirradiation in methanol because protonic solvents when irradiated are known to exert appreciable acid reaction[5]. Instead of rearrangement, these ketones underwent dimerisation. The formation of such dimers and their structural ellucidation are reported in this note.

p-Tolyl *β*-(2-furyl)vinyl ketone (**2**) on irradiation with light from a high pressure Hg lamp through pyrex filter gave the dimer **6**. The dimeric structure (**6**) was based upon its PMR and mass spectra. Its mass spectrum not only showed the molecular weight of the product to be 424, twice that of **2** but also exhibited a most intense peak at *m/z* 212 indicating monomer formation under electron impact. Its PMR spectrum did not show any vinylic proton (as present in **2**) but exhibited multiplets in the high field region at δ 4.8 and 4.1 due to a new group of protons in conformity with the structure **6**. The stereochemistry of **6** became clear on reduction with sodium borohydride in ethanol when it gave the diol **13** whose symmetrical structure was supported by PMR spectrum. The diol **13** underwent dehydration in DMSO giving the ether **14** which showed the proximity of the hydroxy groups and supported the stereostructure **6**. Thus, the dimer was formed by head to head joining of the vinyl bond giving the *cis-anti-cis* structure **6**. The generality of this reaction was observed when similar furyl vinyl ketones **1**, **3** and **4** on irradiation under similar condition afforded the corresponding dimers **5**, **7** and **8**.



The dye-sensitized photooxidation of **1**, **2**, **3** and **4** in the presence of rose bengal gave the corresponding lactones (**9**, **10**, **11** and **12**). Their structures were established by PMR and mass spectral data. But a similar photooxidation of the dimers produced intractable gums, from which no crystalline matter could be isolated.

Benzalacetophenones are known to give dimer-

† Contribution No. 345

ic cyclobutanes[6], but usually mixtures of stereomers are produced. The formation of a single dimeric product stereoselectively from furyl vinyl ketones is therefore a remarkable finding.

Aryl β-(2-furyl)vinyl ketones (**1-4**): *General procedure*

These were prepared by condensing the corresponding acetophenones with furfural in the presence of methanolic KOH. Their characterization data are as follows:

Phenyl β-(2-furyl)vinyl ketone (**1**): Pale yellow needles, m.p. 38-40° (lit.[7] m.p. 40-41°).

p-Tolyl β-(2-furyl)vinyl ketone (**2**): Yellow needles, m.p. 74-75° (lit.[7] m.p. 72-75°).

p-Anisyl β-(2)-furyl)vinyl ketone (**3**): Yellow needles, m.p. 90-92° (lit[7]. m.p. 93°).

p-Chloro β-2-furylvinyl ketone (**4**): Yellow needles, m.p. 80-81° (Found: C, 65.5; H, 5.0. $C_{13}H_{12}O_2Cl$ requires C, 65.8; H, 5.1%) MS: *m/z* 235 (M^+); PMR($CDCl_3$): δ 8.04 (*s*, 1H, Ar−H), 7.9 (*s*, 1H, Ar−H), 7.58 (*s*, 3H, Ar−H & −CO−CH=CH−), 7.25 (*d*, 1H, H_5, *J*= 1.5 Hz), 6.7 (*d*, 1H, H_3, *J*= 3.5 Hz), 6.5 (*m*, 1H, H_4).

Irradiation of aryl β-(2-furyl)vinyl ketones: Formation of dimers

A solution of aryl β-(2-furyl)vinyl ketone (1 g) in methanol (500 ml) was irradiated at room temperature with a high pressure Hg lamp in a quartz vessel for 6-8 hr when the reaction appeared to be 80% complete (TLC). The product was separated from the unchanged starting mayerial by column chromatography on silica gel and purified by crystallisation from solvents. The characterization data of the dimers thus obtained are given below:

Dimer **5**: Colourless needles from methanol, m.p. 72-75° (Found: C, 78.5; H, 5.0. $C_{26}H_{20}O_4$ requires C, 78.8; H, 5.1%); MS: *m/z* 396 (M^+); PMR($CDCl_3$): δ 7.9-7.5 (*m*, 10H, Ar−H), 7.32 (*d*, 2H, H_5 & $H_{5'}$, *J*= 3.5 Hz), 6.32 (*d*, 2H, H_3 & $H_{3'}$, *J*= 2 Hz), 6.18 (*q*, 2H, H_4 & $H_{4'}$), 4.8 (*m*, 2H, H_α & $H_{\alpha'}$), 4.00 (*m*, 2H, H_β & $H_{\beta'}$).

Dimer **6**: Colourless prisms from methanol, m.p. 111-12° (Found: C, 80.5; H, 5.2. $C_{28}H_{24}O_4$ requires C, 80.4; H, 5.4%); MS: *m/z* 424 (M^+), 212 ($M^+/2$); PMR($CDCl_3$): δ 8.00-7.60 (*m*, 8H, Ar−H), 7.40 (*d*, 2H, H_5 & $H_{5'}$, *J*= 1.5 Hz), 6.55 (*d*, 2H, H_3 & $H_{3'}$, *J*= 3.5 Hz), 6.28 (*q*, 2H, H_4 & $H_{4'}$), 4.80 (*m*, 2H, H_α & $H_{\alpha'}$), 4.00 (*m*, 2H, H_β & $H_{\beta'}$), 2.38 (*s*, 6H, 2 × CH_3).

Dimer **7**: Colourless needles from benzene, m.p. 122-25° (Found: C, 73.5; H, 5.4. $C_{28}H_{24}O_6$ requires C, 73.7; H, 5.3%), MS: *m/z* 456 (M^+); PMR($CDCl_3$): δ 8.0-7.5 (*m*, 8H, Ar−H), 7.40 (*d*, 2H, H_5 & $H_{5'}$, *J*= 1.5 Hz), 6.32 (*d*, 2H, H_3 & $H_{3'}$, *J*= 3.5 Hz), 6.13 (*q*, 2H, H_4 & $H_{4'}$), 4.8 (*m*, 2H, H_β & $H_{\beta'}$), 3.9 (*m*, 2H, H_α & $H_{\alpha'}$), 3.82 (*s*, 6H, 2 × OCH_3).

Dimer **8**: Colourless prisms from methanol, m.p. 118-19° (Found: C, 65.9; H, 5.2. $C_{26}H_{24}O_4Cl_2$ requires, C, 65.8; H, 5.1%); MS: *m/z* 470 (M^+); PMR($CDCl_3$): δ 8.0-7.5 (*m*, 8H, Ar−H), 7.28 (*d*, 2H, H_5 & $H_{5'}$, *J*= 1.5 Hz), 6.32 (*d*, 2H, H_3 & $H_{3'}$, *J*= 3.5 Hz), 6.15 (*q*, 2H, H_4 & $H_{4'}$), 4.7 (*m*, 2H, H_β & $H_{\beta'}$), 3.9 (*m*, 2H, H_α & $H_{\alpha'}$).

Photooxidation of aryl β-(2-furyl) vinyl ketones: General method

The furyl ketone (500 mg) in methanol (100 ml) containing rose bengal (20 mg) was irradiated with tungsten lamps (600 W) while a gentle stream of air bubbled through the solution. After the reaction was complete, the solvent was removed under reduced pressure and the photooxidation product isolated by column chromatography over silicagel.

The characterisation of the products are as follows:

Photooxidation product **9**: A colourless amorphous solid from methanol, m.p. 110-11° (Found: C, 68.5; H, 5.0. $C_{14}H_{12}O_4$ requires C, 68.9; H, 4.9%); MS: *m/z* 244 (M^+); PMR($CDCl_3$): δ 8.0-7.6 (*m*, 5H, Ar−H), 7.42 (*d*, 1H, −CO−C*H*=CH, *J*= 2 Hz) 7.22 (*d*, 1H, −CO−CH=C*H*, *J*= 2 Hz), 6.82 (*d*, 1H, H_3, *J*= 3 Hz), 6.25 (*d*, 1H, H_4, *J*= 2 Hz), 4.00 (*s*, 3H, OCH_3).

Photooxidation product **10**: Pale yellow amorphous solid from methanol, m.p. 133-34° (Found: C, 69.5; H, 5.6. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%); MS: *m/z* 258 (M^+); PMR($CDCl_3$): δ 8.0-7.42 (*m*, 4H, Ar−H), 7.28 (*d*, 1H, −CO−C*H*=CH, *J*= 2 Hz), 6.92 (*d*, 1H, −CO−CH=C*H*, *J*= 2 Hz), 6.45 (*d*, 1H, H_3, *J*= 3.5 Hz), 6.28 (*d*, 1H, *J*= 3.5 Hz), 3.68 (*s*, 3H, OCH_3), 3.56 (*s*, 3H, CH_3).

Photooxidation product **11**: Colourless amorphous solid from benzene, m.p. 140-41° (Found: C, 65.9; H, 5.3. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%); MS: *m/z* 274 (M^+), PMR($CDCl_3$): δ 8.0-7.3 (*m*, 4H, Ar−H), 7.15 (*d*, 1H, −CO−CH=C*H*, *J*= 2 Hz), 6.55 (*d*, 1H, H_3, *J*= 3.5 Hz) 6.18 (*d*, 1H, H_4, *J*= 3.5 Hz), 3.98 (*s*, 3H, OCH_3), 3.52 (*s*, 3H, Ar−OCH_3).

Photooxidation product **12**: Colourless prisms from methanol, m.p. 172-75° (Found: C, 59.5; H,

4.6. $C_{14}H_{14}O_4Cl$ requires C, 59.8; H, 5.0%); MS: *m/z* 281 (M^+); PMR($CDCl_3$): δ 8.0-7.6 (*m*, 1H, Ar−H), 7.3 (*d*, 1H, $-CO-CH=CH-$, $J=2$ Hz), 7.0 (*d*,1H, $-CO-CH=CH$, $J=2$ Hz),6.9 (*d*, 1H, H_3, $J=3.5$ Hz), 6.32 (*d*, 1H, H_4, $J=3.5$ Hz), 3.32 (*s*, 3H, OCH_3).

Chemical reduction of the dimer **2**

An ice cooled solution of **2** (500 mg) in ab. ethanol (25 ml) was treated with stirring with sodium borohydride (500 mg). After 1 hr stirring,the reaction mixture was diluted with water and neutralized with acetic acid and the product extracted with ether. The extract was dried (Na_2SO_4), solvent distilled off and the residual solid crystallised from benzene-hexane to give **13** as colourless needles, m.p. 120-21° (Found: C, 78.4; H, 6.7, $C_{28}H_{28}O_4$ requires C, 78.5; H, 6.5%); MS: *m/z* 428 (M^+); PMR($CDCl_3$): δ 8.0-7.4 (*m*, 8H, Ar−H), 7.3 (*d*, 2H, $H_{5\,\&\,5'}$, $J=2$ Hz), 6.55 (*d*, 2H, $H_{3\&3'}$, $J=3.5$ Hz), 6.28 (*q*, 2H, $H_{4\&4'}$), 5.27 (*d*, 2H, $2\times -CHOH$, $J=2$ Hz), 4.35 (*m*, 2H, $H_{\alpha\&\alpha'}$) 3.95 (*m*, 2H, $H_{\beta\&\beta'}$), 3.30 (*s*, 6H, $2\times CH_3$).

Dehydration of the diol **13**: *Formation of the ether* **14**

A solution of the diol **13** (100 mg) in DMSO (5 ml) was heated at 180° for 12 hr then cooled, diluted water and extracted with ether. The extract was dried (Na_2SO_4), solvent distilled off and the product **14** isolated by preparative TLC as a colourless liquid, yield 30 mg (Found: C, 31.5; H, 6.5. $C_{28}H_{26}O_3$ requires C, 82.0; H, 6.3%); MS: *m/z* 410 (M^+); PMR($CDCl_3$): δ 8.00-7.60 (*m*, 8H, Ar−H), 7.40 (*d*, 2H, $H_{5\&5'}$, $J=2$ Hz), 6.80 (*d*, 2H, $H_{4\&4'}$, $J=3$ Hz), 6.5 (*q*, 2H, $H_{3\&3'}$), 4.50 (*m*, 2H, $H_{\alpha\&\alpha'}$), 4.00 (*m*, 2H, $H_{\beta\&\beta'}$) 3.60 (*d*, 2H, $-2H$, $-O-CH-$, $J=5$ Hz), 2.42 (*s*, 6H, $2\times CH_3$).

References

1 Thewalt K & Rudolph W, *Chem Ber*, **96** (1963) 136.

2 Short F W & Rockwood G M, *J heterocyclic Chem*, **6** (1969) 713.

3 Popp F D, Schleigh W R & Katz L E, *J Chem Soc (C)*, 2253 (1968).

4 Vijayasarathy P R & Krishna Rao G S, *Indian J Chem*, **11** (1973) 301.

5 Pearson R G & Dillion R L, *J Am chem Soc*, **75** (1953) 2439. 2439.

6 Sabbe H & Bremer K, *J prakt Chem*, **123** (1929) 1.

7 Stobbe H & Bremer K, *Ber dt Chem Ges*, **39** (1926) 2254.

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One-pot Oxidation & Dehydration with Selenium Dioxide

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The phthalic anhydride derivative (**2**) has been synthesized from Diels-Alder adduct (**1**) by one-pot oxidation with selenium dioxide in acetic anhydride or treatment with N-bromosuccinimide in the presence of sodium acetate in acetic acid.

The allylic hydroxylation of olefins with selenium dioxide is a well studied reaction[1]. SeO_2 combined with pyridine makes allylic hydroxylation possible with conservation of the ethylene-ketal protecting group[2]. In the presence of H_2O_2 only catalytic amount of the above oxidation reagent is necessary[3]. We report herein one-pot oxidative dehydration of a tetrahydrophthalic anhydride derivative (**1**) to yield the corresponding phthalic anhydride (**2**) using selenium dioxide.

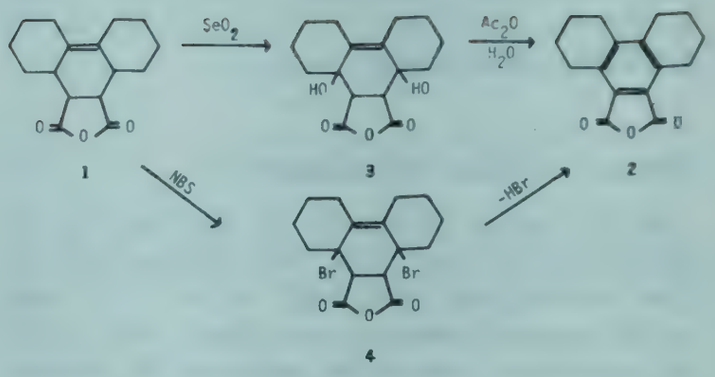
When the Diels-Alder adduct (**1**), prepared in a good yield by the Diels-Alder reaction of di-$\Delta^{1,1}$-cyclohexene[4] with maleic anhydride[5], was heated with excess SeO_2 in refluxing acetic anhydride for 12 hr, **2** was obtained. The formation of **2** may occur via initial allylic hydroxylation of **1** to **3**. According to Guillemonat's rules[6] oxidation of a tertiary CH to the corresponding alcohol is difficult to accomplish relative to a CH_3 or a CH_2 group, and often leads to the conjugated diene through dehydrogenation. Under the above reaction conditions it was possible to obtain **2**, presumably via dehydration of the intermediate diol (**3**) (Scheme 1).

Compound **2** has also been obtained from **1** using N-bromosuccinimide (NBS) and sodium acetate in glacial acetic acid[5]. In this case the formation of **2** is explained by the intermediate dibromide (**4**) and subsequent HBr elimination (Scheme 1).

The structure of **2** was confirmed by direct comparison (PMR, IR, UV, m.p.) with an authentic sample[7].

3,4,5,6-*Dicyclohexanephthalic anhydride* (**2**): (*a*) *With selenium dioxide in acetic anhydride*

A mixture containing **1** (2g, 7.75 mmol), SeO_2 (0.9 g, 11.25 mmol) in acetic anhydride (10 ml)



Scheme 1

was refluxed for 12 hr. After cooling, solid obtained was filtered, dissolved in $CHCl_3$ and again filtered. Evaporation of $CHCl_3$ under reduced pressure left a yellow solid (1.2 g, 61% yield), which was dried *in vacuo* and recrystallized from ethanol to give analytically pure **2**; m.p. 298°; PMR (90 MHz; $CDCl_3$): δ 3.31-3.03 (*m*, 4H, 3-H, 10-H), 2.90-2.51 (*m*, 4H, 6-H, 7-H), 2.12-1.62 (*m*, 8H, 4-H, 5-H, 8-H, 9-H); IR(KBr): 2940, 2880, 1820, 1755, 1285, 1192, 1160, 905, 755 cm^{-1}; UV(CH_3OH): 232 (log ε 3.08).

(*b*) *With NBS and sodium acetate in acetic acid*

A mixture of **1** (2 g, 7.75 mmol), NBS)2.46 g, 13.8 mmol) and absolute CCl_4 (150 ml) was refluxed for 3 hr. After cooling, sodium acetate (1.15 g, 14 mmol) and glacial acetic acid (1.5 m l) were added and the mixture was refluxed for 18 hr. Upon addition of water (100 ml) a yellow precipitate was formed, which was filtered and dried *in vacuo* (400 mg). The organic phase was separated and the solvent removed under reduced pressure. The resulting red-yellow oil solidified on trituration after adding a small amount of CCl_4 (400 mg); total yield of **2** 800 mg (40.6%); m.p. 298°.

References

1 Fieser L & Fieser M, *Reagents for organic synthesis*, Vol. 1 (John Wiley, New York), 1967, 994.
2 Camps F, Coll J & Parente A, *Synthesis*, (1978) 215.
3 Coxon J M, Dansted E & Hartshorn M P, *Org Synth*, **56** (1977) 25.
4 Gruber E F & Adams R, *J Am chem Soc*, **57** (1935) 2555.
5 Greidinger D S & Ginsburg D, *J org Chem*, **22** (1957) 1406.
6 Guillemonat A, *Ann Chim*, **11** (1939) 143.
7 Ginsburg A G, Milovanov V N, Setkina V N & Kursanov D N, *Zh Org Khim*, **3** (1967) 1024; *Chem Abstr*, **67** (1967) 116747.

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A Convenient Synthesis of Substituted Indoles Using Montmorillonite Clay as Catalyst

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Substituted indoles have been synthesised by the reaction of appropriate phenylhydrazine with suitable ketones using montmorillonite clay as catalyst.

In recent years montmorillonite clay has found many applications in organic synthesis[1]. Due to its acidic nature we envisaged that it could as well be used, instead of Lewis acids, in Fischer indole synthesis. The results reported in this note provide experimental proof to our expectation.

In a typical reaction phenylhydrazine (5 g; 0.46 mol) and the ketone (5.32 g; 0.46 mol) were stirred with montmorillonite clay (1 g) for 5 min and then heated at 120° for 5 min. The reaction mixture was extracted with benzene, the organic extract concentrated and the residue subjected to silica gel chromatography and/or crystallisation to afford pure indoles, which are listed in Table 1. All the compounds were characterised by UV, IR, PMR and finally by comparison with authentic samples prepared by conventional way[2-4].

The above method affords substituted indoles in one step, without separation of hydrazones.

The authors thank Prof B B Biswas and Prof (Mrs) P Chakrabarti for their interest in the work.

References

1 Jackson A H, Pandey R K, Nagaraja Rao K R & Roberts E, *Tetrahedron Lett*, (1985) 793.
2 Baccolini G & Todesco P E, *Chem Commun*, (1981) 563.
3 Chakraborty D P, Das K C & Basak S P, *J Indian chem Soc*, **45** (1968) 84.
4 Chakraborty D P, Das K C & Chowdhury B K, *Phytochemistry*, **8** (1969) 733.

Table 1—Products Obtained in Reaction of Ketones with Phenylhydrazines in Presence of Montmorillonite Clay

Starting ketones	Product	m.p. °C	Yield %
	Reaction with phenylhydrazine		
CH_3COCH_3	2-Methylindole	61	65
$C_6H_5COCH_3$	2-Phenylindole	188	65
$CH_3CH_2COC_2H_5$	2-Ethyl-3-methylindole	65	60
$C_6H_5CH_2COC_6H_5$	2,3-Diphenylindole	124	60
Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	116	65
3-Methylcyclohexanone	3-Methyl-1,2,3,4-tetrahydrocarbazole	260	65
	Reaction with (p) $CH_3C_6H_4NHNH_2$		
Cyclohexanone	6-Methyl-1,2,3,4-tetrahydrocarbazole	141	65
	Reaction with (p) $CH_3OC_6H_4NHNH_2$		
4-Methylcyclohexanone	6-Methoxy-3-methyl-1,2,3,4-tetrahydrocarbazole	110	65

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Reactions of Thioamide Vinylogs with Isonitriles

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The Thioamide vinylogs derived from secondary amines (**1**) react with both alkyl and arylisonitriles (**2**) resulting in the formation of 3-N-substitutedamino-1-phenylpropen-1-thione (**3**).

Several reports are available on the nucleophilic[1-4], electrophilic[5-7] and cycloaddition reactions[8-12] of thioamide vinylogs, a group of reactive synthetic intermediates which yield a wide variety of heterocyclic compounds. Also, isonitriles are found to react with 1,3-diazabutadienes in a (1+4) cycloaddition manner[13]. Keeping this and our general interest in the chemistry of sulphur-containing heterodienes[14] in view, we have presently examined the reactions of thioamide vinylogs (**1**) with isonitriles.

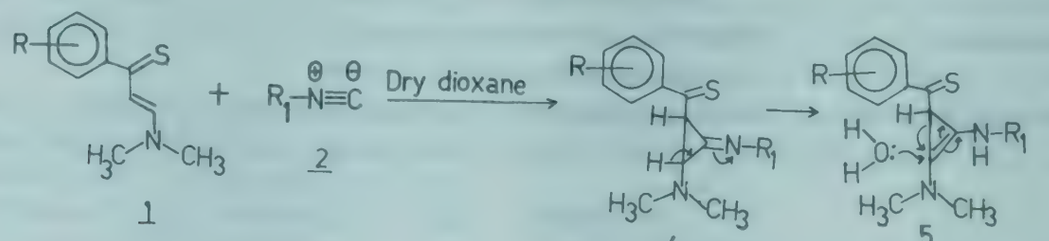
Thioamide vinylogs[15] (**1**) derived from secondary amines and various alkyl- and aryl-isonitriles[16] were prepared by literature methods.

A mixture of 3-dimethylamino-1-phenylpropen-1-thione (**1a**, 0.5 g, 0.0026 mol) and phenylisonitrile (0.3 g, 0.0029 mol) was refluxed in dry dioxane for 4 hr. The solvent was removed under reduced pressure and the product so obtained (0.4 g, 70%) was recrystallised from ethanol and characterised as **3a**, m.p. 102° (lit.[17], m.p. 105-6°); IR: 1640, 1580, 1480 (Found: N, 5.5, Calc. for $C_{15}H_{13}NS$: N, 5.9%); MS: *m/z* 239 (M^+).

Reactions of all other isonitriles (**2**) with **1** were carried out in a similar manner and the products obtained are listed in Table 1.

The products have been assigned structure (**3**) on the basis of analytical results and spectral evidences. The PMR spectra of compounds **3**, in general, display two doublets of one-proton each at δ 6.50-6.65 and 7.60-7.75 assignable to the vinylic protons H_a and H_b respectively. This is expected as the vinylic proton H_b is less shielded because of the deshielding effect of nitrogen attached to the carbon bearing this proton. The multiplet in the region δ 7.10-7.90 is assigned to the aromatic protons and a broad peak at 13.50-15.40 which is exchangeable with D_2O is assigned to the NH proton. In the case of compounds **3e-3g** the methylene protons appear as a doublet at δ 4.50 (J=Hz) probably because of the splitting of these protons by NH proton attached to it. In the case of **3h-3k** the methine protons appear as unresolved multiplets at δ 3.25 and methylene protons as multiplets in the region 1.30-2.10. All these propenes (**3**) have been assigned *cis*-geometry on the basis of coupling constant of two vinylic protons (J_{ab} = 7-8 Hz).

Rationalisation of formation of **3** is outlined in Scheme 1. It is presumed that thioamide vinylogs (**1**) initially undergo (1+2) cycloaddition reaction



3a: R=H, R_1=C_6H_5
b: R=p-CH_3, R_1=C_6H_5
c: R=p-Cl, R_1=C_6H_5
d: R=p-Br, R_1=C_6H_5
e: R=H, R_1=CH_2-C_6H_5
f: R=p-Cl, R_1=CH_2-C_6H_5
3g: R=p-Br, R_1=CH_2-C_6H_5
h: R=H, R_1=Cyclohexyl
i: R=p-CH_3, R_1=Cyclohexyl
j: R=p-Cl, R_1=Cyclohexyl
k: R=p-Br, R_1=Cyclohexyl

Scheme 1

Table 1—Characterisation Data of **3**

Compd	R	m.p. (°C) (lit. m.p.)	Yield (%)	Mol. formula (M^+)	N (%) Found	N (%) Calc.
			$R_1 = C_6H_5$			
3a	H	102 (105-6)[17]	70	$C_{15}H_{13}NS$ (239)	5.54	5.86
3b	*p*-CH_3	124	72	$C_{16}H_{15}NS$ (253)	5.45	5.53
3c	*p*-Cl	128	78	$C_{15}H_{12}ClNS$ (273)	4.73	5.12
3d	*p*-Br	135	80	$C_{15}H_{12}BrNS$ (318)	3.98	4.40
			$R_1 = CH_2 - C_6H_5$			
3e	H	71	62	$C_{16}H_{15}NS$ (253)	5.21	5.53
3f	*p*-Cl	85	70	$C_{16}H_{14}ClNS$ (287)	4.06	4.87
3g	*p*-Br	80	68	$C_{16}H_{14}BrNS$ (332)	3.62	4.22
			R_1 = Cyclohexyl			
3h	H	105	68	$C_{15}H_{19}NS$ (245)	4.61	5.71
3i	*p*-CH_3	100	75	$C_{16}H_{21}NS$ (259)	3.95	4.41
3j	*p*-Cl	100	72	$C_{15}H_{18}ClNS$ (279)	4.80	5.01
3k	*p*-Br	136	75	$C_{15}H_{18}BrNS$ (324)	4.16	4.32

with isonitriles leading to iminocyclopropane intermediate (**4**) which in turn isomerises to aminocyclopropene intermediate (**5**). This intermediate **5** undergoes hydrolytic cleavage to afford **3** with the extrusion of a molecule of dimethylformamide.

References

1 Guemas J P, Reliquet A, Reliquet F & Quiniou H, *C r hebd sèanc Acad Sic Paris*, **288** (C) (1979) 89.

2 Bignebat J, Quiniou H & Lozac'h N, *Bull Soc Chim Fr*, (1966) 1699.

3 Tang S C, Koch S, Weinstein G N, Lane R W & Holm R H, *Inorg Chem*, **12** (1973) 2589.

4 Bard M, Duguay G & Quiniou H, *C r hebd sèanc Acad Sci Paris*, **274** (C) (1972) 1641.

5 Clesse F & Quiniou H, *C r hebd sèanc Acad Sci Paris*, **272** (C) (1971) 326.

6 Meslin J C & Quiniou H, *C r hebd sèanc Acad Sci Paris*, **273** (C) (1971) 148.

7 Meslin J C, N'Guessan Y T, Quiniou H & Tonnard F, *Tetrahedron*, **31** (1975) 2679.

8 Malayer C & Duguay G, *C r hebd sèanc Acad Sci Paris*, **273** (C) (1971) 1457.

9 Bard M, Meslin J C & Quiniou H, *Chem Commun*, (1973) 672.

10 Pradère J P & Quiniou·H, *C r hebd sèanc Acad Sci Paris*, **275** (C) (1972) 677.

11 Pradere J P, N' Guessan Y T, Quiniou H & Tonnard F, *Tetrahedron*, **31** (1975) 3059.

12 Pradère J P, Quiniou H, Rabiller C & Martin G J, *Bull Soc Chim Fr*, (1976) 991.

13 Matsuda I, Yamamoto S & Ishii Y, *J chem Soc Perkin Trans-I*, (1976) 1523.

14 Baruah P D, Roy G, Satsangi R & Mahajan M P, *Indian J Chem*, **25B** (1986) 357.

15 Lin Yang-i & Lang (Jr) S A, *J org Chem*, **45** (1980) 4857.

16 William P, Weber & George W Gokel, *Tetrahedron Lett*, (1972) 1637.

17 Leaver D, Mckinnon D M & Robertson W A H, *J chem Soc*, (1965) 32.

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A New Synthesis of 3-Chlorocoumarins & Synthesis of Isocoumestan

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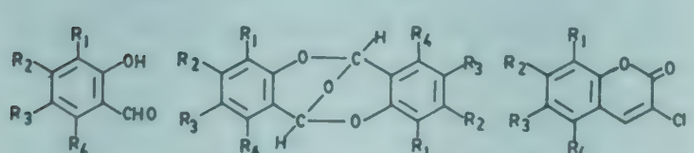
The preformed complex of $POCl_3$ and N,N-diethylchloroacetamide (**1**) on reaction with substituted salicylaldehydes (**2a-e**) yields 3-chlorocoumarins (**4a-c**) while with *o*-hydroxybenzophenones (**5a-c**) the products obtained have been characterised as 3-chloro-4-arylcoumarins (**6a-c**). 3-Chloro-4-(2′-hydroxyphenyl)coumarin (**6d**) on treatment with aq. KOH yields isocoumestan (**7**).

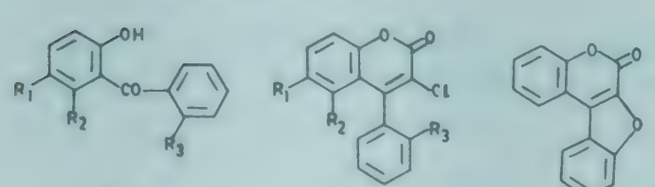
Recently we have developed a general method[1,2] for the synthesis of 3-methyl-, 3-phenyl- and 3-phenoxy-coumarins. This method has now been utilised for the synthesis of 3-chloro- and 3-chloro-4-phenylcoumarins.

A preformed complex[1,2] of N,N-diethylchloroacetamide (**1**) and $POCl_3$, was allowed to react with different salicylaldehydes (**2a-e**) in chloroform at room temperature. Hydrolysis with aq. $NaHCO_3$ furnished two products in each case, which were separated by chromatography over silica gel column. Elution with petroleum ether afforded the disalicylaldehyde (**3a-c**) in the case of **2a-c**, which were characterised by spectral data and in the case of known compounds such as **3a** and **3b** by comparing their melting points with those reported in literature[3-5].



2 **3** **4**

2-4 a $R_1=R_2=R_3=R_4=H$
b $R_1=R_2=H$, $R_3, R_4=-CH=CH-CH=CH-$
c $R_1=R_2=R_4=H$, $R_3=CH_3$
d $R_1=OCH_3$, $R_2=R_3=R_4=H$
e $R_1=R_3=R_4=H$, $R_2=OCH_3$



5 **6** **7**

5-6 a $R_1=R_2=R_3=H$
b $R_1=CH_3$ $R_2=R_3=H$
c $R_1, R_2=-CH=CH-CH=CH-$, $R_3=H$
d $R_1=R_2=H$, $R_3=OH$

Elution with light petroleum-EtOAc (19:1) afforded 3-chlorocoumarins (**4a-e**) the structures of which were confirmed from spectral data and comparison with reported[6] m.ps (Table 1). The coumarins **4d** and **4e** are being synthesised for the first time.

Benzophenones (**5a-c**) on reaction with preformed complex of **1** and $POCl_3$ at 95-105° in the absence of solvent, gave hitherto unknown coumarins (**6a-c**) in ~40% yield. These compounds **6a-c** were characterised by their mode of formation, IR, PMR and analytical data.

The above method has been extended for the synthesis of isocoumestan (**7**). Benzophenone (**5d**)[7] was converted into chlorocoumarin (**6d**) which on cyclisation with alcoholic KOH afforded **7**. Compound (**7**) was found to be identical (m.p., m.m.p., co-TLC, co-IR) with an authentic sample. The one-pot conversion of benzophenone (**5d**) resulted in improved yield of **7**. It may be pointed out that of the four known methods[8-11] for the synthesis of isocoumestans only a recent method has similar applicability[11].

General procedure for 3-*chlorocoumarins* (**4a-e**)

$POCl_3$ (0.01 mol) was added to N,N-diethylchloroacetamide (0.01 mol) at 0° to form a yellowish complex. To this, substituted salicylaldehyde (**2**,0.01 mol) in dry $CHCl_3$ (10 ml) was added in one lot and the mixture refluxed. After completion of the reaction (TLC) the solvent was distilled off, the mixture was cooled, poured into aq. Na_2CO_3 (10%, 25 ml), warmed for 15 min, cooled and acidified. It was extracted with chloroform (3 × 10 ml), the organic extract washed with water (2 × 10 ml), dried (Na_2SO_4) and concentrated. Column chromatography of the residue over silica gel using light petroleum gave disalicylaldehydes (**3a-c**) while 3-chlorocoumarins (**4a-e**) were obtained from light petroleum-EtOAc (19:1) eluates. The yields and m.p. of the products and the spectral data of the unknown compounds are reported in Table 1.

3-*Chloro*-4-*aryl coumarins* (**6a-d**)

2-Hydroxybenzophenones (**5a-d**) on reaction with preformed complex of **1** and $POCl_3$ at 95-105° in the absence of solvent afforded **6a-d**.

Table 1—Physical and Spectral Data for 3-Chlorocoumarins and Disalicylaldehydes

Compd	Yield (%)	m.p. (lit) °C	PMR($CDCl_3$ + TMS) δ ppm
3a	25	130 (130)[3]	—
3b	31	240 (242-43)[5]	—
3c	38	139	2.28 (6H, *s*, $-CH_3$), 6.2 (2H, *s*, 2-O−CH−O−), 6.52 (2H, *d*, *J*=8 Hz, Ar−H), 7.0 (2H, *dd*, *J*=8 & 2 Hz, Ar−H), 7.04 (2H, *bs*, Ar−H)
4a	36	121 (121-23)[6]	—
4b	24	166-67 (169)[6]	—
4c	25	120 (121-22)[6]	—
4d	35	153	3.97 (3H, *s*, $-OCH_3$), 6.96-7.34 (3H, *m*, Ar−H), 7.82 (1H, *s*, C_4−H)
4e	30	164	3.85 (3H, *s*, $-OCH_3$), 6.79 (1H, *bs*, C_8−H), 6.9 (1H, *dd*, *J*=8 & 2 Hz, C_6−H), 7.32 (1H, *d*, *J*=8 Hz, C_5−H), 7.75 (1H, *s*, C_4−H)
6a	39	144	7.08-7.6 (9H, *m*, Ar−H)
6b	39	135	2.3 (3H, *s*, $-CH_3$), 6.81 (1H, *s*,C_5−H), 7.28-7.6 (7H, *m*, Ar−H)
6c	40	185	7.3-8.3 (11H, *m*, Ar−H)
6d	40	166	5.65 (1H, *s*, −OH, exchanges with D_2O), 7.1-7.6 (8H, *m*, Ar−H)

Isocoumestan (**7**)

Compound (**6d**) (0.1 g) was refluxed in alc. KOH (0.25 g in 5 ml) for 5 hr, diluted with water acidified with conc. HCl and warmed on a water-bath (80-90°) for 1 hr. The reaction mixture was cooled, extracted with ether (2×15 ml), dried (Na_2SO_4) and concentrated. The solid thus obtained (0.072 g, 83%) was recrystallised from chloroform to yield **7**, m.p. 168-69° (lit.[11] m.p. 169-70°).

Alternate procedure for **7**

To the preformed complex of **1** (0.02 mol) and $POCl_3$ (0.02 mol) was added 2,2′-dihydroxybenzophenone (**5d,** 0.02 mol) and the mixture heated in an oil-bath at 100° for 11 hr. The reaction mixture was poured into aq. KOH (10%, 10 ml), warmed on a water-bath for 5 hr, cooled, acidified (conc. HCl) and warmed on a water-bath (80-90°) for 1 hr. The reaction mixture was cooled, extracted with chloroform (3×25 ml), dried and evaporated. Column chromatography of the residue over silica gel using light petroleum gave **7**, yield 30% (identical with **7** obtained above).

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References

1 Phadke C P, Kelkar S L & Wadia M S, *Synth Commun*, **14** (1984) 407.
2 Salunke P S, Phadke C P, Kelkar S L & Wadia M S, *Synthesis*, (1985) 111.
3 Adams R, Fogler M F & Kreger C W, *J Am chem Soc*, **44** (1922) 1126.
4 Khalaf A A, *Bull Fact Sci*, **2** (1973) 237; *Chem Abstr*, **85** (1974) 20260.
5 Jones P R & Gelinas R M, *J org Chem*, **46** (1981) 194.
6 LeCorre M, *Ann Chim*, **14** (1968) 193; *Chem Abstr*, **70** (1969) 3749.
7 Baddar F G, Eliassal L S & Baghas V B, *J chem Soc*, (1955) 1714.
8 King H I, Holland R H, Reed F P & Robertson A, *J chem Soc*, (1948) 1672.
9 Chatterjea J N, Achari K & Jain N C, *J Indian chem Soc*, **47** (1970) 590.
10 Someswari N, Srihari K & Sundaramurthy V, *Synthesis*, (1977) 609.
11 Joshi U K, Kelkar R M & Paradkar M V, *Indian J Chem*, **23B** (1984) 456.

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Synthesis of 2,3-Dihydro-9*H*-furo[3,2-*b*]-benzopyran-9-ones by Claisen Rearrangement of 3-(3-Methylbut-2-enyloxy)-chromones

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The Claisen rearrangement of 3-(3-methylbut-2-enyloxy)chromone (**2a**) in N,N-dimethylaniline at 170-75°C yields the normal open-chain product 2-(1,1-dimethylallyl)-3-hydroxychromone (**3a**). However, rearrangement of **2a** in N,N-diethylaniline at 200-205°C yields the isomeric abnormal open-chain product 2-(1,2-dimethylallyl)-3-hydroxychromone (**4a**). Acid catalysed cyclisation of **3a** and **4a** gives 2,3-dihydro-2,3,3-trimethyl-9*H*-furo[3,2-*b*]benzopyran-9-one (**5a**) and 2,3-dihydro-2,2,3-trimethyl-9*H*-furo[3,2-*b*] benzopyran-9-one (**6a**) respectively. Similar rearrangement of 3-(3-methylbut-2-enyloxy)-6-methylchromone (**2b**) in N,N-dimethylaniline at 170-75°C yields a mixture of normal **3b** and abnormal open-chain product **4b**; while 3-(3-methylbut-2-enyloxy)-8-methylchromone (**2c**) under similar conditions yields only the normal open-chain product (**3c**). Acid catalyzed cyclization of **3b** and **3c** give **5b** and **5c** respectively.

Though much work on the Claisen rearrangement of 3-(3-methylbut-2-enyl)ethers of coumarins[1], xanthones[2], flavones[3,4] and related compounds[4,5] have been reported, similar Claisen rearrangement of 3-(3-methylbut-2-enyloxy)chromones does not seem to have been carried out. In this note we present results of Claisen rearrangement of 3-(3-methylbut-2-enyl)ethers of 3-hydroxy-(**1a**), 3-hydroxy-6-methyl-(**1b**)- and 3-hydroxy-8-methyl-(**1c**)-chromones. The rearrangement products were isolated, their structures determined, and then cyclised to the corresponding dihydrofuro compounds.

The ethers (**2a-c**) were prepared in 40% yields by the condensation of **1a-c**[6,7] with 3-methylbut-2-enyl bromide in K_2CO_3/KI and acetone medium (reflux 3 hr). The structrues of **2a-c** were established on the basis of correct elemental analyses and spectral data (IR and PMR). The yields, melting points and solvent of crystallisation are given in Table 1. The PMR spectral data of the representative **2a** are as follows:

2a; δ 1.70, 21.75 [*s* each, 3H each, $>C(CH_3)_2$], 4.57 (*d*, 2H, J=7 Hz, $-O-CH_2$, 5.44 (*m*, 1H, $=CH$), 7.30-7.67 (*m*, 3H, Ar−H), 7.73 (*s*, 1H, C_2-H), 8.25 (*dd*, 1H, J=9, 1Hz, Ar−H).

Table 1—Physical Data of Compounds **2a-c, 3a-c, 4a, 4b, 5a-c** and **6a**

Compd	m.p. (°C)	Solvent of crystallisation	Yield (%)
2a	62	Pet. ether (60-80°)	90
2b	49-50	Pet. ether	90
2c	Colourless oil		90
3a	78-79	Pet. ether:Benzene	70
3b	95-96	Pet. ether	13
3c	73-74	Pet. ether	84
4a	96-98	Pet. ether	76
4b	118-19	Pet. ether	12
5a	125	Pet. ether	80
5b	98-99	Pet. ether:Benzene	—
5c	122	Pet. ether	—
6a	115-16	Pet. ether:Benzene	80

Satisfactory elemental analyses were obtained for all the compounds.

Claisen rearrangement of **2a** in N,N-dimethylaniline at 170-75°C for 4 hr yielded the normal open chain product 2-(1,1-dimethylallyl)-3-hydroxychromone (**3a**). Rearrangement of **2a** in N,N-diethylaniline at 200-205°C for 2 hr furnished the isomeric abnormal open chain product 2-(1,2-dimethylallyl)-3-hydroxychromone (**4a**). Rearrangement of the ether (**2b**) in N,N-dimethylaniline at 170-75°C for 5 hr furnished **3b** and **4b** while **2c** gave only **3c** under similr conditions.

Attempts to cyclise **3a** and **4a** in HCl/AcOH medium were unsuccessful and the starting material was recovered unchanged. However prolonged heating of **3a** and **4a** in HBr/AcOH (30%) medium (heating on water-bath, 10 hr) yielded the corresponding cyclised products 2,3-dihydro-2,3,3-trimethyl-9*H*-furo[3,2-*b*]benzopyran-9-one (**5a**) and 2,3-dihydro-2,2,3-trimethyl-9*H*-furo-[3,2-*b*]benzopyran-9-one (**6a**) respectively. The difficulty in cyclisation may be due to strong chelation of 3-hydroxyl group with chromone carbonyl. Treatment of **3b** and **3c** with HBr/AcOH yielded the corresponding cyclised products **5b** and **5c**. The structures of **3a-c, 4a-c, 5a-c** and **6c** were supported by analytical and spectral data. The PMR data of the representative structures **3a, 4a, 5a** and **6a** are as follows:

PMR spectrum of **3a** displayed signals at δ 1.53 [*s*, 6H, $>C(CH_3)_2$], 4.97-5.18 (*m*, 2H, $=CH_2$), 6.20 (*q*, 1H, J=17, 10Hz, $=CH-$), 6.47

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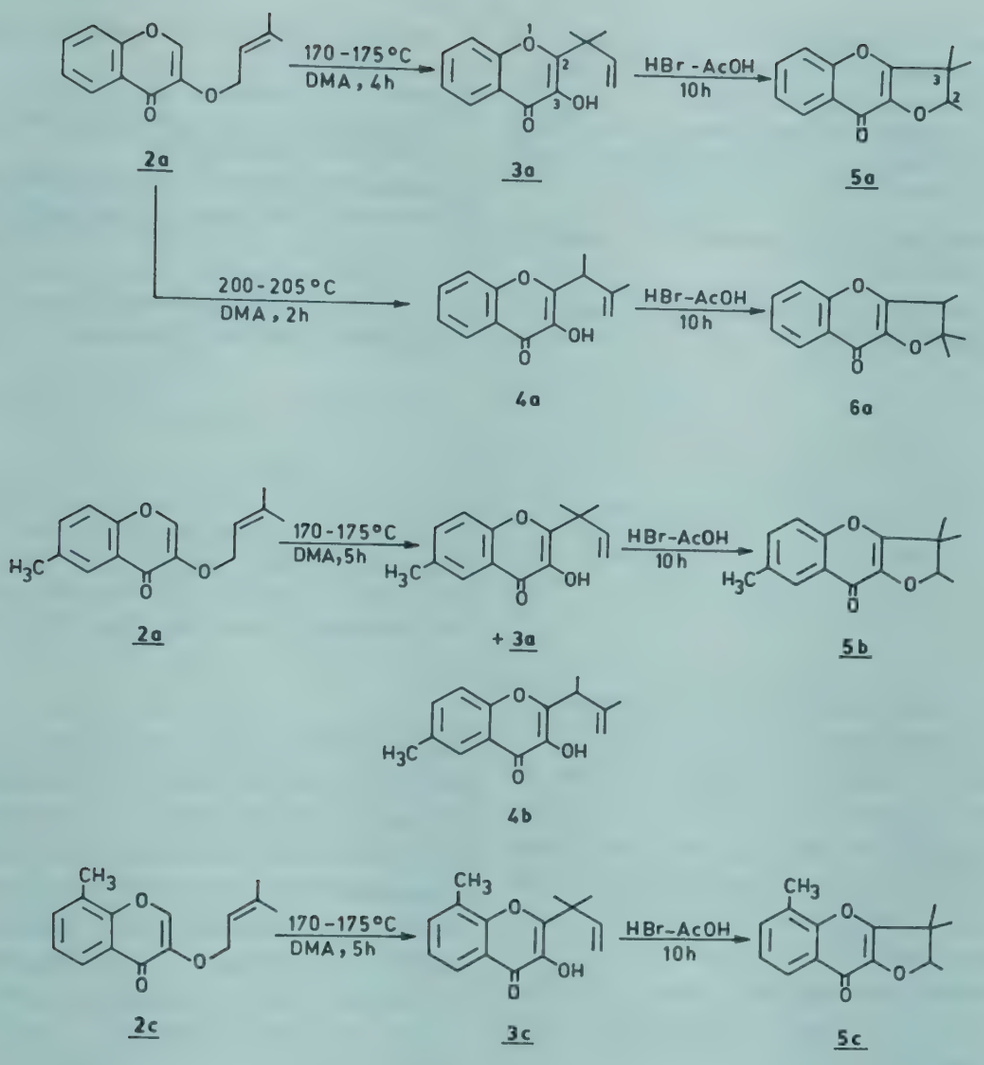

(*bs*, 1H, C_3-OH), 7.23-7.70 (*m*, 3H, Ar−H) and 8.20 (*dd*, 1H, *J*=9, 1Hz, Ar−H), while **4a** showed signals at δ 1.73 (*s*, 3H, $=C(-CH_3)-$), 1.45 (*d*, 3H, *J*=7 Hz, $>CH-CH_3$), 3.94 (*m*, 1H, $>CH-CH_3$), 4.86 (*bs*, 2H, $=CH_2$), 6.45 (*bs*, 1H, C_3-OH), 7.20-7.60 (*m*, 3H, Ar−H) and 8.16 (*dd*, 1H, *J*=9, 2 Hz, Ar−H). Similarly the PMR spectrum of **5a** exhibited signals at δ 1.28 (*s*, 3H), 1.47 [*s*, 3H, $>C(CH_3)_2$], 1.45 (*d*, 3H, *J*=7 Hz, $-CH-CH_3$), 44.5 (*q*, 1H, *J*=7 Hz, $-O-CH(CH_3)$), 7.30-7.70 (*m*, Ar−H) and 8.31 (*dd*, 1H, *J*=9, 2Hz, Ar−H). The PMR of **6a** had signals at δ 1.32 (*s*; 3H), 1.48 [*s*, 3H, $>C(CH_3)_2$], 1.21 [*d*, 3H, *J*=7 Hz, $-CH-(CH_3)$], 3.25 (*q*, 1H, *J*=7 Hz, $-CH-CH_3$), 7.18-7.50 (*m*, 3H, Ar−H) and 8.28 (*dd*, 1H, *J*=9, 2Hz, Ar−H). These values are in agreement with the reported data[1-5].

As oxygen heterocyclics having 1,1-dimethylallyl substituents and fused 2,3,3-trimethyldihydrofuran ring system occur in nature[8], the products isolated in this study can be of use as model compounds in the structural elucidation and synthesis of natural products.

The rearrangement products and their cyclised products were tested for antibacterial activity against three types of bacteria, *Staphylococcus aureus*, *Salmonella typhosa*, *Escherchia coli*, by tube dilution method[9] at concentrations 200 μg/ml, 100 μg/ml, 50 μg/ml and 25 μg/ml. **2a** was found to be active against *Salmonella typhosa* at 200 μg/ml (partial inhibition) but **3c** was active at all concentrations on *Staphylococcus aureus*; **5a, 5b, 5c** and **6a** were shownto possess partial activity at 200 μg/ml on *Salmonella typhosa*.

We thank Prof H Polasa and M Gopal Reddy for *in vitro* studies.

References

1 Murray R D H & Ballantyne M M, *Tetrahedron*, **26** (1970) 4667; Ballantyne M M, Murray R D H & Penrose A B, *Tetrahedron Lett*, (1968) 4155; Murray R D H, Ballantyne M M, Hagg T C & McCabe P H, *Tetrahedron*, **31** (1975) 2960; Jain A C, Kumar A & Khazanchi R, *Indian J Chem*, **16B** (1978) 1039.

2 Dyer A, Jefferson A & Scheinmann F, *J org Chem*, **33** (1968) 1259; Burling E D, Jefferson A & Scheinmann F, *Tetrahedron*, **21** (1965) 2653; Jain A C & Anand S M, *J chem Soc Perkin Trans I*, (1974) 329; Locksley H D, Quillinan A J & Scheinmann F, *J chem Soc (C)*, (1971) 3804.

3 Ahuja M, Bandopadhyay M & Seshadri T R, *Indian J Chem*, **11** (1973) 723.

4 Subba Raju K V, Sudha K & Srimannarayana G, *Indian J Chem*, **19B** (1980) 866.

5 Jain A C, Tuli D K & Khazanchi R, *Indian J Chem*, **16B** (1978) 973.

6 Arndt F & Kallner G, *Ber*, **57** (1924) 202; Chandraprakash Reddy K, Veeramallaiah B & Srimannarayana G, *Curr Sci*, **49** (1980) 18.

7 Collonge J & Guyot A, *Bull Soc chim Fr*, (1958) 1325.

8 Murakami T, Hagiwara M, Tanaka K & Chen C M, *Chem pharm Bull*, **21** (1973) 1851; Vishwakarma R A, Kapil R S & Popli S P, *Indian J Chem*, **22B** (1983) 612.

9 Neippi L, *Experimental chemotherapy*, Vol. 21 (Academic Press, New York), 1964, 169.

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Synthesis of 5-Chloro-2,2,4,6-tetramethylindane, a Synthon for a Sesquiterpenic Fungal Metabolite†

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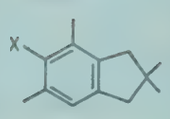
Synthesis of 5-chloro-2,2,4,6-tetramethylindane (**3**) is described. 2,2-Dimethylation of the known indanone (**6**), followed by reduction gives the trimethylindane (**7**). Birch reduction of **7** and subsequent acid hydrolysis leads to a mixture of α,β- and β,γ-unsaturated enones (**8**). Vilsmeier-Haack reaction on **8** affords the indanecarboxaldehyde (**9**) which is then reduced to **3**.

From the cultured mycelium of the fungus *Fomitopsis insularis*, Nozoe *et al.*[1] isolated and interesting sesquiterpene alcohol (**1**), biogenetically related to the protoilludane and marasmane skeletons. In an earlier study[2] we reported that cyclohexenones conveniently afford chlorobenzenecarboxaldehydes on Vilsmeier-Haack reaction, a finding which has now been exploited in the synthesis of the chloroindane (**3**), a potential synthon for the natural product **1**. Dugan *et al.*[3] synthesized a related indane (**2**) from *m*-xylene, in connection with the structure elucidation of marasmic acid.

5-Methoxy-6-methylindan-1-one[4] (**6**) was converted into the methoxytrimethylindane (**7**) by 2,2-dimethylation[5] with NaH and excess of CH_3I followed by Wolff-Kishner reduction[6]. Birch reduction[7] of **7** and subsequent acidic hydrolysis of the resulting dihydro compound[7] gave a mixture of α,β- and β,γ-unsaturated ketones (**8**). Vilsmeier reaction[2] on **8** gave the chloroindanecarboxaldehyde (**9**) which on Wolff-Kishner reduction[6] furnished **3**. However, lithiation of **3** to **4** by treatment with *n*-butyllithium[8] or its conversion to the corresponding arylmagnesium chloride (**5**) for subsequent reaction with ethylene oxide to generate the β-hydroxyethyl side chain affording **1** failed, despite several attempts, apparently due to steric reasons.

Details of instrumentation used, spectral and other data presentation and the extractive work-up of reactions are as mentioned in reference 9.

†Part LXXXII in the series, Studies in Terpenoids, Part LXXXI, Raju B & Krishna Rao G S, *Indian J Chem*, **26B** (1987)



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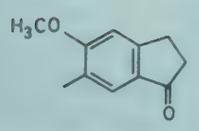
3, X = Cl
4, X = Li
5, X = MgCl



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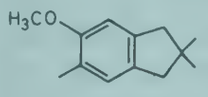

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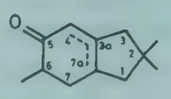

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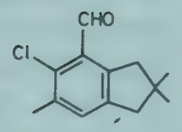

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5-Methoxy-2,2,6-trimethylindane (**7**)

To **6** (17.6 g, 0.1 mol), NaH (2.4 g, 0.2 mol, freed from mineral oil) in dry DMF (120 ml) was added in one lot with stirring. The reaction mixture after stirring at room temperature for 0.5 hr was cooled in ice-bath and CH_3I (30 g, 0.2 mol) in DMF (60 ml) added dropwise and stirring continued for 12 hr at room temperature. Extractive work-up after dilution with water (500 ml) gave the dimethylated product of **6** as an oil (15 g, 71%); b.t. 105°/1.5 mm; IR(film): 1700 (C=O), 1610 (aromatic); PMR($CDCl_3$): 1.2 (*s*, 6H, H_3CCCH_3), 2.26 (*s*, 3H, Ar−CH_3), 2.83 (*s*, 2H, Ar−CH_2), 3.66 (*s*, 3H, OCH_3) and 7.06 (*bs*, 2H, 2×Ar−H).

A mixture of **6** (14.28 g, 0.07 mol), hydrazine hydrate (4.0 g, 0.08 mol), NaOH (4.5 g, 0.1 mol) and diethylene glycol (200 ml) was warmed (water-bath) till the solid NaOH dissolved. Then it was heated to reflux for 15 hr. Extractive work-up after dilution with water (500 ml) gave **7** as an oily liquid (7.5 g, 56%); b.t. 85°/1.5 mm; IR(film): 1610, 1590 (aromatic), 1480, 1460; PMR(CCl_4): 1.13 (*s*, 6H, H_3CCCH_3), 2.1 (*s*, 3H, Ar−CH_3), 2.53 (*bs*, 4H, 2×Ar−CH_2), 3.66 (*s*, 3H, OCH_3), 6.43 (*s*, 1H, Ar−H_4) and 6.73 (*s*, 1H, Ar−H_7) (Found: C, 82.0; H, 9.6. $C_{13}H_{18}O$ requires C, 82.1; H, 9.5%).

2,2,6-Trimethyl-6,7-dihydro-$\Delta^{3a,4}/\Delta^{7a,3a}$*-inden-5(2H)-one* (**8**)

To distilled liquid NH_3 (200 ml), **7** (6.8 g, 35 mmol) in dry THF (10 ml) was added. To this solution *t*-butanol (10 ml) was added, followed by thinly cut Li (0.35 g) during 5 hr till the blue colour persisted. The reaction was quenched with

methanol when the colour disappeared. Ammonia was allowed to evaporate and to the residue water (200 ml) added. Extractive work-up gave the reduced compound[7]; IR(film) 1720 (enol ether), 1660 (C=C); PMR(CCl_4): 1.08 (*s*, 6H, H_3CCCH_3), 1.62 (*s*, 3H, vinyl-CH_3), 2.06 (*bs*, 4H, 2×allylic-CH_2) 2.58 (*bs*, 4H, 2×doubly allylic-CH_2) and 3.46 (*s*, 3H, OCH_3).

To the above compound in ether (100 ml), dil. HCl (10%, 30 ml) was added and the mixture stirred at room temperature for 1 hr. It was diluted with water (100 ml). Extractive work-up gave **8** as viscous liquid (4.3 g, 75%), b.t. 125°/1.5 mm; IR (film): 1710 (β,γ-unsaturated C=O), 1660 (α,β-unsaturated C=O); PMR(CCl_4): 1.02-1.04 (*m*, 9H, H_3CCCH_3 and $CHCH_3$), 1.6-3.04 (*m*, CH_2 and $CHCH_3$) and 5.7 (*bs*, vinylic-CH) (Found: C, 81.0; H, 9.5. $C_{12}H_{18}O$ requires C, 81.3; H, 9.7%).

5-*Chloro*-2,2,6-*trimethylindane*-4-*carboxaldehyde* (**9**)

Vilsmeier reagent was prepared by the dropwise addition of $POCl_3$ (2.3 g, 1.5 mmol) with stirring to DMF (5.8 g, 80 mmol) at 0-5°. The stirring was continued at room temperature for 0.5 hr. To this, **8** (1.64 g, 10 mmol) in DMF (4 ml) was added in one portion. The reaction mixture was heated on a water-bath for 6 hr, cooled, poured into ice-cold aq. NaOAc (10%, 30 ml) and heated on a water-bath for 20 min to decompose the complex. Extractive work-up gave **9** as a colourless liquid (0.8 g, 36%), b.t. 110°/1.5 mm; IR(film): 1690 (C=O); PMR(CCl_4): 1.06 (*s*, 6H,H_3CCCH_3), 2.32 (*s*, 3H, Ar−CH_3), 2.58 (*s*, 2H, Ar−CH_2), 2.98 (*s*, 2H, Ar−CH_2 *peri* to CHO), 7.20 (*s*, 1H, Ar−H) and 10.52 (*s*, 1H, CHO) (Found: C, 70.5; H, 6.9. $C_{13}H_{15}OCl$ requires C, 70.1; H, 6.8%).

5-*Chloro*-2,2,4,6-*tetramethylindane* (**3**)

A mixture of **9** (0.66 g, 3 mmol), hydrazine hydrate (2 g, 4 mmol), NaOH (0.45 g, 10 mmol) and diethyleneglycol (10 ml) was warmed on a water-bath till the NaOH pellets dissolved. The reaction mixture was heated to reflux for 10 hr and poured into a large excess of water (100 ml). Extractive work-up, after saturating the aqueous phase with NaCl, gave after purification by chromatography (SiO_2 column, elution with pet. ether), **3** as a mobile liquid (0.35 g, 56%), b.t. 80°/1.5 mm; IR(film): 1470, 1000; PMR(CCl_4): 1.10 (*s*, 6H, H_3CCCH_3), 2.24 (*s*, 3H, Ar−CH_3), 2.32 (*s*, 3H, Ar−CH_3) 2.64 (*s*, 4H, 2×Ar−CH_2) and 6.84 (*s*, 1H, Ar−H) (Found: C, 75.0; H, 8.3. $C_{13}H_{17}Cl$ requires C, 74.8; H, 8.2%).

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References

1 Nozoe S, Kobayashi H, Urano S & Furukawa J, *Tetrahedron Lett*, (1977) 1381.

2 Raju B & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 177.

3 Dungan J J, de Mayo P, Nisbet M, Robinson J R & Anchel M, *J Am chem Soc*, **38** (1966) 2828.

4 Kulkarni S N, Patil S B, Panchangam P V & Nargund K S, *Indian J Chem*, **5** (1967) 471; Fieser L F & Lothrop W C, *J Am chem Soc*, **58** (1936) 2050.

5 McMorris T C, Liu M & White R H, *Lloydia*, **40** (1977) 221.

6 Grundon M F, Henbest H B & Scott M D, *J chem Soc*, (1963) 1855.

7 Birch A J & Subba Rao G S R, *Adv org Chem*, **8** (1972) 58.

8 Sharp P R, Astruc D & Schrock R R, *J organomet Chem*, **182** (1979) 477.

9 Raju B & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 712.

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Vilsmeier-Haack Reaction on Some 3-Buten-2-ols

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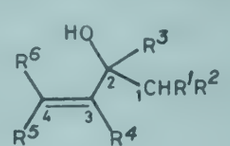
Vilsmeier-Haack reaction on 3-buten-2-ols (**1b-i**) leads to benzene mono-, di- and tricarboxaldehydes (**3-8**) in yields ranging from 6-26%. The presence of at least five appropriate participating carbon atoms on the butenol backbone (**1b-n**) seems to be essential for formylative benzocyclization to occur.

The Vilsmeier-Haack reaction on 4-aryl-3-buten-2-ols (**1a**) has been reported[1a] to give 5-arylpenta-2,4-dienals (**2**, R = H, CH_3) (Scheme 1). The present communication shows that the rection leads to benzocyclization, when either R^5 or R^6 are alkyl groups (no specific geometry *E/Z*, of the double bond is implied). The products (**3-8**) (Scheme 1) thus resulting from **1b**[2], **1c**[3], **1d**[4], **1e**[5], **1f**[6], **1g**[7], **1h**[8] and **1i**[9] are uniquely characterized by formylative benzocyclizations.

A mixture of isophthalaldehyde[10] (**3**) and benzene-1,3,5-tricarboxaldehyde[11] (**4**) (4:1) obtained by the Vilsmeier reaction on 3-penten-2-ol (**1b**) was separated by column chromatography (SiO_2, pet. ether-ethyl acetate, 5:1). The structure assignment for the product, 5-ethylisophthalaldehyde (**5**)



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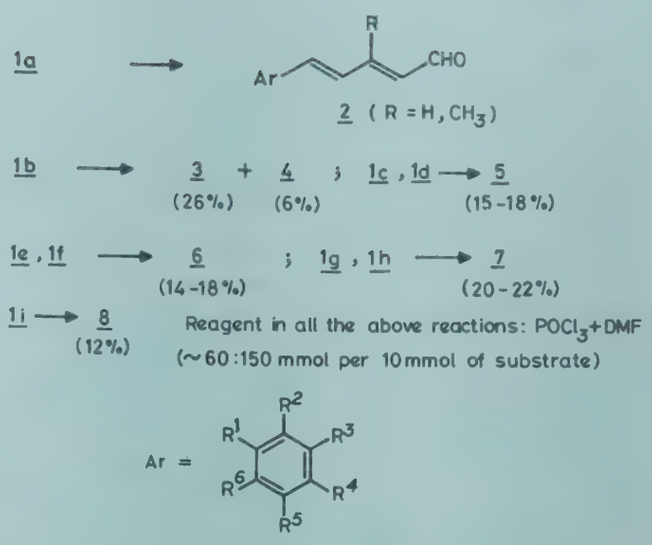
1	R^1	R^2	R^3	R^4	R^5	R^6
a	H	H	H, CH_3	H	Ar	H
b	H	H	H	H	CH_3	H
c	H	H	H	H	n-C_3H_7	H
d	H	C_2H_5	H	H	CH_3	H
e	H	CH_3	H	H	C_2H_5	H
f	H	H	H	CH_3	C_2H_5	H
g	CH_3	CH_3	H	H	CH_3	H
h	H	CH_3	H	H	CH_3	CH_3
i	H	H	CH_3	H	CH_3	CH_3
j	H	C_2H_5	H	H	H	H
k	H	H	H	H	C_2H_5	H
l	H	H	H	CH_3	CH_3	H
m	H	CH_3	H	H	CH_3	H
n	H	H	H	H	CH_3	CH_3



	R^1	R^2	R^3	R^4	R^5	R^6
3	CHO	H	CHO	H	H	H
4	CHO	H	CHO	H	CHO	H
5	CHO	H	CHO	H	C_2H_5	H
6	CHO	H	CH_3	H	CH_3	H
7	CHO	CH_3	CHO	H	CH_3	H
8	CHO	H	CHO	CH_3	H	CH_3

Scheme 1

from the alkenols (**1c** and **1d**) is based on its spectral data and elemental analyses. The product (**6**) from the alkenols (**1e** and **1f**), characterized as 3,5-dimethylbenzaldehyde[12], is identical with an authentic specimen obtained earlier in this laboratory by the Vilsmeier reaction on 3,5-dimethyl-1,4-dihydrobenzoic acid[13]. The alkenols (**1g** and **1h**) gave 2,5-dimethylisophthalaldehyde (**7**), identical with an authentic sample obtained from 1,4-dimethyl-1,4-cyclohexadiene[14] by Vilsmeier reaction. The alkenol (**1i**) gave 4,6-dimethylisophthalaldehyde (**8**), identical with the product obtained from 4,6-bischloromethyl-*m*-xylene[15] by Sommelet reaction. The Vilsmeier-Haack reaction on the alkenols (**1i-m**), giving 5-methylisophthalaldehyde[16] and the alkenol (**1n**), giving a mixture of 4-methylisophthalaldehyde and 2-methylbenzene-1,3,5-tricarboxaldehyde, have already been reported[17].

Thus from the behaviour of the butenols (**1b-n**) in the Vilsmeier-Haack reaction, the presence of at least five appropriate participating carbon atoms on the butenol backbone appears to be a prerequisite for formylative benzocyclization to occur. No attempt has been made in the present study either to optimize the yields of **3-8** or to isolate the intermediate iminium salts prior to their cyclization[11c] leading ultimately to **3-8**.

Vilsmeier reaction on 1-ethyl-4-methyl-3-buten-2-ol (**1d**): *General procedure*

To a solution of **1d** (1.14 g, 10 mmol) in DMF (11.2 ml, 150 mmol) at 0°C was added under stirring $POCl_3$ (5.5 ml, 60 mmol) during 15 min and the bath temperature was slowly raised to 80°C. The reaction mixture was finally heated for 6 hr on a boiling water-bath, cooled, poured onto crushed ice (10 g) containing aq. NaOAc (20%, 30 ml). After leaving it aside at room temperature for 5-6 hr, the product was extracted with ether (25 ml × 4). The combined extract was washed successively with water, aq. Na_2CO_3 (10%, 40 ml) and water and dried (Na_2SO_4). Removal of solvent, purification of the residue by column chromatography (SiO_2, pet. ether-ethyl acetate, 10:1), and crystallization from pet. ether gave **5**; yield 0.29 g (18%), m.p. 45°; IR(nujol): 1690 and 1595 cm^{-1}; PMR (60 MHz, CCl_4); 1.36 (*t*, J=8 Hz, 3H, CH_3), 2.85 (*q*, J=8 Hz, 2H, CH_2), 7.92 (*bs*, 2H, Ar−H_4 & H_6), 8.11 (*bs*, 1H, Ar−H_2), 10.1 (*s*, 2H, 2×CHO); MS: *m/z* 162 (M^+) (Found: C, 74.2; H, 6.0. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%).

References

1 (a) Parameswara Reddy M & Krishna Rao G S, *Synthesis*, (1980) 815.
(b) *cf.* Jutz C & Heinicke R, *Chem Ber*, **102** (1969) 623.
2 Arbuzov Y A & Pisha T A, *Doklady akad Nauk*, **116** (1957) 71; *Chem Abstr*, **52** (1958) 6357.
3 Sturtz G & Pondaven R A, *Tetrahedron Lett*, (1978) 629.
4 Grenwood F L, *J org Chem*, **24** (1959) 1735.
5 Martin G J, Naulet N, Lefevere F & Martin M L, *Org Magn Reson*, **4** (1972) 121.
6 Chuit C, Foulon J P & Normant J F, *Tetrahedron*, **36** (1980) 2305.
7 Magid R M, Fruchey O S, Johnson W L & Allen T G, *J org Chem*, **44** (1979) 359.
8 Colonge J & Reymermier M, *Bull soc Chim Fr*, (1956) 188.
9 Ernst H V & Hoffmann H M R, *Chem Ber*, **114** (1981) 1464.
10 *Atlas of spectral data and physical constants for organic compounds*, Vol. II, edited by J.G. Grasselli & W M Ritchey (C R C Press, Ohio) 1975, b 1151.
11 (a) Reid W & Konigstein F J, *Chem Ber*, **92** (1959) 2532.
(b) Zemlicka J, Krupicka J & Arnold Z, *Colln Czech chem Commun*, **27** (1962) 2464.
(c) Holy A & Arnold Z, *Colln Czech chem Commun*, **30** (1965) 33.
(d) Cochrane W P, Pauson P L & Stevens T S, *J chem Soc (C)*, (1968) 630.
12 *Dictionary of organic compounds*, edited by J Buckingham (Chapman and Hall, London) 1982, p. 2074.
13 Raju B & Krishna Rao G S, *Synthesis*, (1987) 197.
14 Raju B & Krishna Rao G S, *Indian J Chem*, (In press).
15 Keller H & Lehner H, *Liebigs Ann Chem*, (1978) 595.
16 Sreenivasulu M, Suresh Chander Rao M & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 173.
17 Sreenivasulu M & Krishna Rao G S, *Indian J Chem*, **26B** (1987) 581.

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Application of Knoevenagel Condensation to 4-Acetamidophenazone Derivatives

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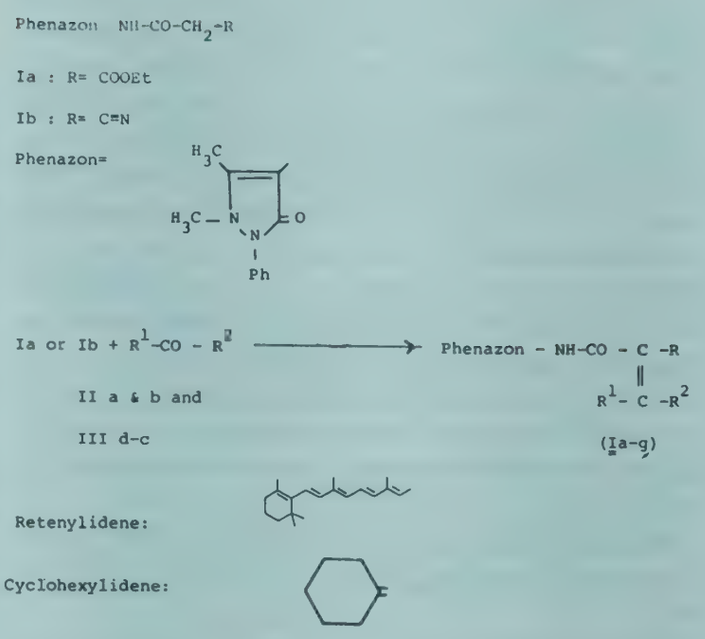
Ethoxycarbonyl-(Ia)- and cyano-(Ib)-acetamidophenazones have been subjected to Knoevenagel condensation with unsaturated aldehydes and ketones. The products obtained are the corresponding α,β-unsaturated esters or cyanide derivatives (**1a-g**). Condensation of Ia,b with *o*-hydroxycarbonyl compounds afford the corresponding coumarins and chromenimines (**2**, **3**and **4**).



The malonamidophenazone ethyl ester (Ia)[1] and some of its diamide and hydrazide derivatives[2] were found to possess better antiinflammatory activity than the reference substance[3]. The chemical reactivity of Ia has earlier been studied[4] in our laboratory by subjecting it to Knoevenagel condensation with saturated aliphatic and aromatic aldehydes. The present investigation deals with the condensation of Ia or its cyano-analogue Ib[5] with unsaturated aldehydes, ketones and their conversion into new types of coumarin derivatives of well known biological interest[6], which otherwise are difficult to prepare by the direct method.

The reaction of Ia,b with unsaturated aldehydes (IIa,b) and ketones (IIIa-c) in ethanol in the presence of piperidine as catalyst led to the corresponding α,β-unsaturated derivatives (**1a-g**) (Table 1). The structures of these products were established on the basis of spectral (IR and PMR) and elemental analysis data. Thus, the IR spectra (KBr) exhibited the $\nu C=O$ modes of the ester moiety at 1700 cm^{-1} in **1a-c** and 1735 cm^{-1} in **1e-g**. In addition **1b,d** displayed $\nu C\equiv N$ around 2220 cm^{-1}. All the compounds displayed the amide-I band in the region 1670-1650 cm^{-1}. The 90 MHz PMR spectra of **1a, b, e, g** in $CDCl_3$ (TMS int. ref.) exhibited two singlets of three protons each at δ 2.1 ($=CCH_3$) and 3.2 (CH_3-N-) and no indication of methylene protons. In addition **1b,d** exhibited a 13-proton multiplet in the region δ 6.8-7.9 due to the aromatic and methine protons (C_6H_5-N-, $C_6H_5-CH=CH-CH=C$) and a D_2O exchangeable one-proton singlet at 5.3 due to the $-NH-CO-$ proton. Compound **1e** showed two singlets of three protons each at δ 1.7 and 1.8 [$=C(CH_3)_2$] while **1g** displayed a 10-proton multiplet due to cyclohexylidene group in the region δ 1.5-1.8.

Treatment of Ia, b with *o*-hydroxyaldehydes (IVa-d) under the same conditions afforded the

Table 1—Characterisation Data of Compounds **1a-g** Obtained by Condensation of Ia,b with Carbonyl Compouns (IIa,b or IIIa-c)

Compd	R	Carbonyl Compound	R^1	R^2	Yield %	m.p. °C	Crystallisation solvent
1a	COOEt	IIa	H	$CH=CH-Ph$	92	192	Methanol
1b	CN	IIa	H	$CH=CHPh$	87	164	Methanol/DMF
1c	COOEt	IIb	H	Retenylidene	62	46	Ether
1d	CN	IIb	H	Retenylidene	57	56	Ether
1e	COOEt	IIIa	CH_3	CH_3	76	137	Ethanol
1f	COOEt	IIIb	CH_3	CH_2-CH_3	73	143	Ethanol
1g	COOEt	IIIc	Cyclohexylidene		67	152	Ethanol/DMF

All the compounds gave satisfactory C, H analyses.

corresponding coumarins (**2a-d**) and chromenimine (**2e-h**) derivatives respectively. Condensation of Ia, b with *o*-hydroxyacetophenone or with methyl salicylate[7] met with failure even on prolonged reflux; the use of sodium ethoxide as catalyst instead resulted in the opening of the amide linkage. However, condensation could be effected in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) as a catalyst, instead of the piperidine, and fusion. The 4-methyl- and 4-hydroxy-coumarins or chromenimine **3a** or **b** and **4a** or **b** respectively were the products (Table 2). The chromenimines **2e-h**, **3b** and **4b** were easily hydrolysed with hydrochloric acid, at room temperature, to the corresponding coumarins **2a-d**, **3a** and **4a** as indicated by TLC[8] (using ethyl acetate-hexane 4/1). All attempts to condense benzoin with either Ia or Ib failed.

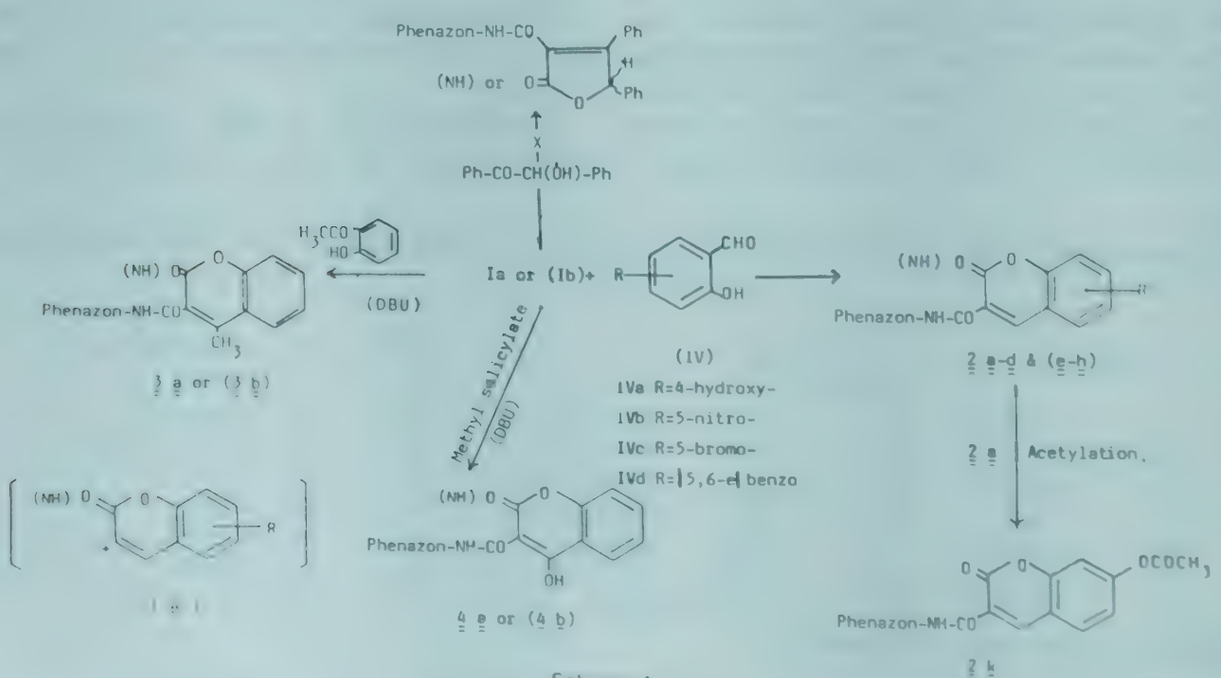
Acetylation of **2a** (Ac_2O/sodium acetate, acetic acid) gave the corresponding 7-acetoxy derivative (**2k**).

The IR spectra of **2**, **3** and **4** indicated the presence of cyclic lactone at 1700-1735 cm^{-1}, in all the cases, which is at lower frequency relative to the 2*H*-benzo-2-one[9] (1760-1770 cm^{-1}) due to the extended conjugation. In addition the band characteristic for the acetoxy group of **2k**, appeared at 1770 cm^{-1}. The PMR spectra of **2a, e, h** and **4b** were of little significance, since most of the protons appeared in the region δ 7.2-7.8, except for the two methyl groups of the pyrazolone ring and C_4-H in **2a, e, h** situated at δ 8.2 which was more deshielded than the corresponding proton of the non-substituted coumarin (δ 7.72) or its calculated value[10]. This is probably due to the amide linkage at C-3 of the lactone ring. In addition, the two exchangeable protons for **2e, h** at δ 11.9 and 9.1 were attributed to the $=NH$ and $-CO-NH-$ respectively.

Table 2—Characterisation Data of Compounds **2a-h, 2k, 3a,b** and **4a,b**

Compd	R	Yield %	m.p. °C	Crystallisation solvent
2a	7-hydroxy-	93	290	DMF
2b	6-nitro-	82	239	Ethanol
2c	3,5-dibromo-	71	230	Methanol/DMF
2d	[5,6-e]benzo-	67	269	Ethanol
2e	7-hydroxy-	95	218	DMF
2f	6-nitro-	80	227	Ethanol
2g	3,5-dibromo-	65	223	Methanol/DMF
2h	[5,6-e]benzo-	63	251	Ethanol
2k	7-acetoxy-	75	271	-Do-
3a		55	237	-Do-
3b		48	219	-Do-
4a		33	194	-Do-
4b		40	171	-Do-

The mass spectra of **2a, d, h** and **4b** exhibited M^+ peaks (rel. abundance 5-20%). The characteristic fragmentation involved cleavage at C-3 of the lactone ring and loss of mass 229 and (or) 230; the corresponding peaks were relatively more abundant (27-87%) and were attributed to the loss of phenazon $-NH-CO-$ moiety either directly or by the loss of phenazon $-NCO-$ and H in two successive steps to give (B)[11] (Scheme 1). These results reflected the relative stable nature of coumarin or chromenimine ring under electron impact. Otherwise, fragmentation was complex



Scheme 1

and showed the loss of $-CO-$ and $-NH-$ moieties simultaneously ($M^+ - 43$) in the case of **2h** and **4b**. The base peak appeared at *m/z* 56 in all the cases.

4-(α-*Arylidene or alkylidene-α-ethoxycarbonyl or cyano-)acetamidophenazone* (**1a-g**)

A mixture of Ia or Ib (1 mmol), the appropriate carbonyl compound (2 mmol), piperidine (0.1 ml) and ethanol (20 ml) was refluxed for 2 hr. The reaction mixture was evaporated to dryness and the residue crystallised from the appropriate solvent (Table 1).

3-(4-*Antipyrinylaminocarbonyl)substituted coumarin or chromenimine* (**2a-h**)

A mixture of Ia or Ib (1 mmol), appropriate *o*-hydroxyaldehyde (1.1 mmol), piperidine (0.1 ml) and ethanol (50 ml) was refluxed for 30 min. The reaction mixture was left overnight in an ice chest and the yellowish coloured precipitate was filtered off and crystallised from the appropriate solvent (Table 2).

3-(4-*Antipyrinylaminocarbonyl)substituted coumrin or chromenimine* (**3a** *or* **b** *and* **4a** *or* **b**)

A mixture of Ia or Ib (1 mmol), *o*-hydroxyacetophenone or methyl salicylate (1.5 mmol) and DBU (0.1 ml) was heated on an oil-bath at 150° with constant stirring, for 10 minutes. Absolute ethyl alcohol (5 ml) was added and the reaction mixture was refluxed overnight. It was concentrated under reduced pressure, the residue dried by successive addition and evaporation of toluene and crystallised from the appropriate solvent (Table 2).

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References

1 Abou Shady H, El-Kerdawy M M & Massoud M A M, *J Pharm Sci, Egypt*, **19** (1978) 207.
2 Abou-Ouf A A, Farghaly A M, El-Kerdawy M M & Massoud M A M, *Indian J Chem*, **16B** (1978) 989.
3 Ferreira S H & Vane J R A, *Rev Pharmac*, **14** (1974) 57.
4 El-Kerdawy M M, Farghaly A M & Massoud M A M, *Proceeding on the First International Conference of Applied Sciences*, Zagazig University, April 1985, p. 133.
5 Ried W & Schleimer B, *Angew Chem*, **70** (1958) 164.
6 Feurer G. *in Progress in medicinal chemistry*, Vol. 10 (Elsevier, Netherlands), 1974, 85.
7 Kawase Y & Sakashita K, *Bull Soc chem Japan*, **35** (1962) 1869.
8 O'Callaghan C N, *J chem Soc*, (1971) 207.
9 Ruiver A & Renson M, *Bull Soc chem Belg*, **79** (1970) 89.
10 Matter U E, Pascual C, Pretsch E, Pross A, Simon W & Sternhell S, *Tetrahedron*, **25** (1969) 2023.
11 Saint-Ruf G, De A, Brunskill J S A & Jeffrey H, *J heterocyclic Chem*, **17** (1980) 81.

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Synthesis of Quinolines via Cyanoethylation

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1,8-Dioxo-1,2,3,4,5,6,7,8-octahydrobenzo[*f*]pyrido[3,2-*h*]quinoline (III) and 4,9-dioxo-1,2,3,4,9,10,11,12-octahydroquinolino-[7,8-*h*]quinoline (VI) have been synthesised respectively via cyanoethylation followed by hydrolysis and cyclisation with polyphosphoric acid.

Synthesis of benzochromanones[1,2] from β-naphthol via cyanoethylation is reported in literature. However, the synthesis of 1,8-dioxo-1,2,3,4,5,6,7,8-octahydrobenzo[*f*]pyrido[3,2-*h*]quinoline (**III**) and 4,9-dioxo-1,2,3,4,9,10,11,12-octahydroquinolino[7,8-*h*]quinoline (**VI**) has not been reported so far. In view of this and in continuation of our earlier work[3-5] on cyanoethylation of naphthols and naphthylamines leading to the synthesis of polycyclic compounds and their further conversion into isoxazole and pyrazole derivatives, we have now synthesised quinolines **III** and **IV** from 2,3- and 1,8-diaminonaphthalenes respectively via cyanoethylation. Some of these compounds arouse special interest due to antimicrobial activity[3] of such compounds.

Cyanoethylation of 2,3-diaminonaphthalene and 1,8-diaminonaphthalene in the presence of acetic acid and acrylonitrile afforded N,N′-bis(2-cyanoethyl)-2,3-diaminonaphthalene (**I**)and N,N′-bis(2-cyanoethyl)-1,8-diaminonaphthalene (**IV**) respectively, which on alkaline hydrolysis gave N,N′-bis(2-carboxyethyl)-2,3-diaminonaphthalene (**II**) and N,N′-bis(2-carboxyethyl)-1,8-diaminonaphthalene (**V**) respectively. The acids **II** and **V** on cyclisation with polyphosphoric acid afforded 1,8-dioxo-1,2,3,4,5,6,7,8-octahydrobenzo[*f*]-pyrido[3,2-*h*]quinoline (**III**) and 4,9-dioxo-1,2,3,4,9,10,11,12-octahydroquinolino[7,8-*h*]quinoline (**VI**) respectively.

Melting points were determined in sealed capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 377 spectrophotometer, mass spectra on a JEOL JMS D-300 instrument and PMR spectra on a 60 MHz Perkin-Elmer R-32 spectrophotometer using TMS as internal standard.

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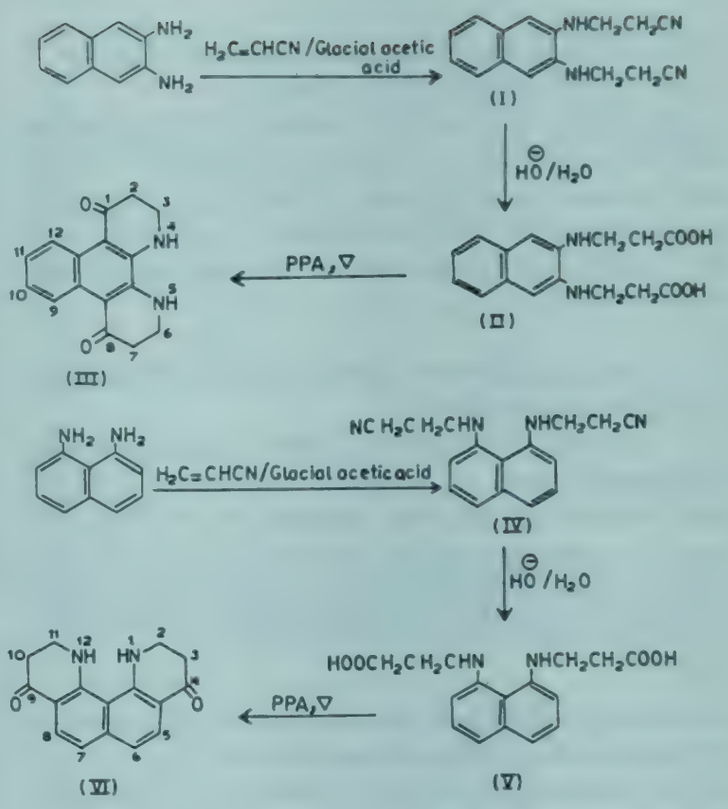

N,N′-Bis(2-cyanoethyl)-2,3-diaminonaphthalene (I) and N,N′-bis(2-cyanoethyl)-1,8-diaminonaphthalene (IV)

A mixture of 2,3-diaminonaphthalene or 1,8-diaminonaphthalene (5.0 g, 0.032 mol), gl. acetic acid (4 ml) and acrylonitrile (10.18 g, 0.2 mol) were cyanoethylated by refluxing on a water-bath for 20 hr. The reaction mixture was extracted with methylene chloride (200 ml), washed with water (150 ml) dried, and solvent removed to give **I** or **IV** as a solid.

Compound **I**: It crystallised from ethanol (3.93 g, 47%), m.p. 240° (d), (Found: C, 72.5; H, 6.4; N, 21.5. $C_{16}H_{16}N_4$ requires C, 72.7; H, 6.1; N, 21.2%); IR: 816, 1292, 1480, 1560, 2222 (C≡N), 3362 (NH) cm^{-1}; PMR($CDCl_3$): δ 2.7-2.9 (*m*, 4H, 2×$-NHCH_2CH_2CN$), 4.1-4.15 (*br*, 2H, 2×NH), 4.2-4.5 (*m*, 4H, 2×$-NH-CH_2CH_2CN$), 6.9-7.75 (*m*, 6H, Ar−*H*), MS: *m/z* 264 ($M^{+\cdot}$).

Compound **IV**: It crystallised from ethanol (4.0 g, 48%), m.p. 222-23° (d) (Found: C, 72.5; H, 6.4; N, 21.5. $C_{16}H_{16}N_4$ requires C, 72.7; H, 6.1; N, 21.2%); IR: 816, 1290, 1480, 1580, 2220 (C≡N), 3360 (NH) cm^{-1}; PMR($CDCl_3$): δ 2.69-3.1 (*m*, 4H, 2×$-NHCH_2CH_2CN$), 4.2-4.25 (*br*, 2H, 2×NH), 4.3-4.45 (*m*, 4H,2×$-NHCH_2CH_2CN$), 7-7.8 (*m*, 6H, Ar−*H*); MS: *m/z* 264 ($M^{+\cdot}$).

N,N-Bis(2-carboxyethyl)-2,3-diaminonaphthalene (II) and N,N-bis(2-carboxyethyl)-1,8-diaminonaphthalene (V)

Compound **I** or **IV** was refluxed with a solution of sodium hydroxide (5.0 g) in (20 ml) water for 15 hr, cooled overnight and acidified with dil. hydrochloric acid. The product was extracted with ether (200 ml) and concentrated to afford **II** or **V**.

Compound **II**: It crystallised from ethanol (3.2 g, 70%), m.p. 270° (d) (Found: C, 63.3; H, 5.7; N, 9.1. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%); IR: 695, 880, 1400, 1578, 1720 (C=O), 3340 (NH) cm^{-1}.

Compound **V**: It crystallised from ethanol, (3.0 g, 65.6%), m.p. 250° (d) (Found: C, 63.3; H, 5.7; N, 9.1. $C_{16}H_{18}N_2O_4$ requires C, 63.6; H, 6.0; N, 9.3%).

1,8-*Dioxo*-1,2,3,4,5,6,7,8-*octahydrobenzo[f]pyrido*-[3,2-*h*]*quinoline (III) and* 4,9-*dioxo*-1,2,3,4,9,10,11,12-*octahydroquinolino*[7,8-*h*]*quinoline (VI)*

The acid **II** or **V** was cyclised with P_2O_5 (40.0 g) and phosphoric acid (16 ml) preheated at 100° for 0.5 hr. The heating was continued for 2 hr with occasional shaking. The mixture was cooled, decomposed with water and extracted with chloroform. The solvent layer was washed with sodium bicarbonate solution (250 ml) and then with water (250 ml), dried and solvent removed afforded the cyclised quinoline **III** or **VI**.

Compound (**III**): It crystallised from ethanol (1.17 g, 65%), m.p. 333° (d) (Found: C, 71.8; H, 5.0; N, 10.2. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%); PMR($CDCl_3$): δ 2.8 (*t*, 4H, 2- and 7-CH_2), 3.4 (*t*, 4H, 3- and 6-CH_2) 7.07-7.5 (*m*, 4H, Ar−*H*), 8.17-8.2 (br, *s*, 2H, 4- and 5-NH), MS: *m/z* 266 ($M^{+\cdot}$).

Compound **VI**: It crystallised from ethanol (2.0 g, 67%), m.p. 320° (d) (Found: C, 71.8; H, 5.4; N, 10.2. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%); IR: 1628, 1680, 1700 (C=O), 3360 (NH) cm^{-1}; PMR($CDCl_3$): δ 2.7-2.9 (*t*, 4H, 3- and 10-CH_2), 3.39-3.5 (*t*, 4H, 2- and 11-CH_2), 7.27-7.8 (*m*, 4H, Ar−*H*), 8.2-8.4 (br *s*, 2H, 1- and 12-NH), MS: *m/z* 266 ($M^{+\cdot}$).

References

1 Backman G B & Levine H A, *J Am Chem Soc*, **69** (1947) 2341.

2 Bell K H & Duewell H, *Aust J Chem*, **16** (1963) 101.

3 Muthusubramanian L & Misra G S, *Eur J Chem*, **21** (1986) 163.

4 Subramanian L M & Misra G S, *Synthesis*, **12** (1984) 1063.

5 Subramanian L M & Misra G S, *Indian J Chem*, **25B** (1986) 199.

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Condensed 1,8-Naphthyridines: Part VIII—Synthesis of 2-Arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones

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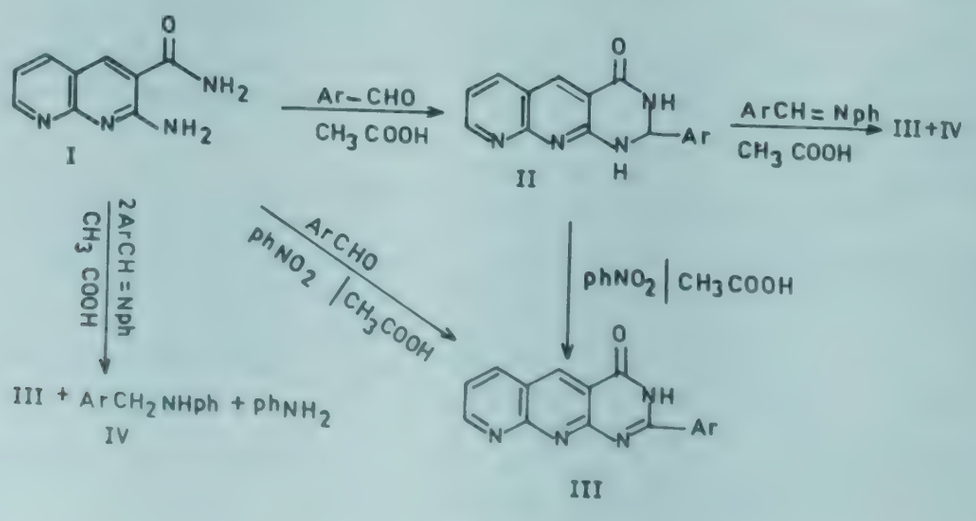
2-Arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones (III) have been synthesized (i) by the oxidation of 2,3-dihydro-2-arylpyrimido[4,5-*b*][1,8]naphthyridin-4(1*H*)-ones (II) with nitrobenzene-acetic acid, which in turn have been obtained by the condensation of 2-amino-1,8-naphthyridine-3-carboxamide (I) with aromatic aldehydes in gl. acetic acid, and (ii) by the condensation of 2-amino-1,8-naphthyridine-3-carboxamide (I) with either aromatic aldehydes in nitrobenzene-acetic acid or schiff bases in gl. acetic acid. The structural assignments of all the products are based on elemental analyses and spectral (IR, mass and PMR) data.

In view of broad spectrum biological activity of 1,8-naphthyridines[1-3] and pyrimidines[4-7] and in continuation of our studies on the synthesis and biological activity of condensed [1,8]naphthyridines[8-12], we have now prepared a number of hitherto unreported 2-arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones (III). The reaction sequence is outlined in Scheme 1.

The starting compound 2-amino-1,8-naphthyridine-3-carboxamide (I) was obtained by the condensation of 2-aminonicotinaldehyde with cyanoacetamide in ethanol containing a catalytic amount of piperidine[13]. Condensation of I with aromatic aldehydes in gl. acetic acid led to the formation of 2,3-dihydro-2-arylpyrimido[4,5-*b*][1,8]-naphthyridin-4(1*H*)-ones (II; Table 1) in good yield. The structures of these compounds were in conformity with their elemental analyses and spectral data (IR, PMR, mass). In the IR spectra, the absence of characteristic bands due to $-CONH_2$ indicated the condensation products to be II. The PMR spectrum of IIc (Ar = *p*-$CH_3-C_6H_4$) in DMSO-d_6 exhibited a three-proton singlet at δ 3.2 due to methyl group, a signal at 5.8 due to benzylic proton indicating the presence of a dihydro system, and a complex multiplet at 6.3-9.6 for two NH and eight aromatic protons.

The oxidation of II with nitrobenzene in gl. acetic acid gave 2-arylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones (III; Table 1). The PMR spectrum of IIIc in DMSO-d_6 exhibited a three-proton singlet at δ 3.3 due to methyl group, multiplets at 9.1, 9.4 and 9.6 due to C-5, C-6 and C-8 protons respectively, a broad hump at 6.4 for NH proton and a complex multiplet at 7.3-8.3 for C_7-H and four aromtic protons. There was no signal due to benzylic proton.

Compounds III were also prepared by the condensation of I with aromatic aldehydes in refluxing nitrobenzene and gl. acetic acid. In an alternative route, compound IIIc (Ar = *p*-$CH_3-C_6H_4$) was obtained in a very good yield by the reaction of I with two mol of benzylideneaniline in acetic acid. Thus, it is clear that benzylideneaniline serves both as an aldehyde source and as a hydrogen acceptor. The reduced product (IVc; Ar = *p*-$CH_3-C_6H_4$) of the schiff base was identified as *p*-methylbenzylaniline by conversion into hydrochloride, (m.p. 188°; lit.[14] m.p. 187-89°). The reaction of IIc with one mol of benzylideneaniline in acetic acid at reflux temperature also gave IIIc and IVc



Scheme 1

Table 1—Characterization Data of Compounds II and III

Compd	Ar	m.p. (°C)	Yield (%)	Mol. formula*	Found (%) (Calc.)		
					C	H	N
IIa	C_6H_5	>300	65	$C_{16}H_{12}N_4O$	69.5	4.1	20.0
					(69.7	4.3	20.3)
IIb	o-$CH_3-C_6H_4$	>300	80	$C_{17}H_{14}N_4O$	70.1	4.9	19.1
					(70.3	4.8	19.3)
IIc	p-$CH_3-C_6H_4$	>300	85	$C_{17}H_{14}N_4O$	70.1	4.7	19.2
					(70.3	4.8	19.3)
IId	o-$OCH_3-C_6H_4$	>300	80	$C_{17}H_{14}N_4O_2$	66.6	4.4	18.0
					(66.7	4.6	18.3)
IIe	$p-OCH_3-C_6H_4$	>300	82	$C_{17}H_{14}N_4O_2$	66.5	4.4	18.1
					(66.7	4.6	18.3)
IIf	o-$Cl-C_6H_4$	>300	72	$C_{16}H_{11}N_4OCl$	61.5	3.2	18.3
					(61.9	3.6	18.1)
IIg	m-$Cl-C_6H_4$	>300	70	$C_{16}H_{11}N_4OCl$	61.6	3.3	18.2
					(61.9	3.6	18.1)
IIh	p-$Cl-C_6H_4$	>300	85	$C_{16}H_{11}N_4OCl$	61.3	3.1	18.0
					(61.9	3.6	18.1)
IIi	o-$OH-C_6H_4$	>300	65	$C_{16}H_{12}N_4O_2$	65.1	4.0	18.9
					(65.8	4.1	19.2)
IIj	o-$NO_2-C_6H_4$	>300	60	$C_{16}H_{11}N_5O_3$	59.2	3.1	21.4
					(59.3	3.4	21.8)
IIk	m-$NO_2-C_6H_4$	>300	65	$C_{16}H_{11}N_5O_3$	59.2	3.1	21.2
					(59.8	3.4	21.8)
III	p-$N(CH_3)_2-C_6H_4$	>300	66	$C_{18}H_{17}N_5O$	67.0	5.1	21.1
					(67.7	5.3	21.9)
IIIa	C_6H_5	>300	60	$C_{16}H_{10}N_4O$	70.3	3.5	20.2
					(70.1	3.6	20.4)
IIIb	o-$CH_3-C_6H_4$	>300	72	$C_{17}H_{12}N_4O$	70.4	4.1	19.3
					(70.8	4.2	19.4)
IIIc	p-$CH_3-C_6H_4$	>300	76	$C_{17}H_{12}N_4O$	70.6	4.1	19.3
					(70.8	4.2	19.4)
IIId	o-$OCH_3-C_6H_4$	>300	75	$C_{17}H_{12}N_4O_2$	67.3	4.0	18.2
					(67.1	3.9	18.4)
IIIe	p-$OCH_3-C_6H_4$	>300	78	$C_{17}H_{12}N_4O_2$	67.2	3.9	18.2
					(67.1	3.9	18.4)
IIIf	o-$Cl-C_6H_4$	>300	75	$C_{16}H_9N_4OCl$	62.0	2.8	18.0
					(62.3	2.9	18.2)
IIIg	m-$Cl-C_6H_4$	>300	72	$C_{16}H_9N_4OCl$	62.0	2.8	18.1
					(62.3	2.9	18.2)
IIIh	p-$Cl-C_6H_4$	>300	78	$C_{16}H_9N_4OCl$	62.1	2.9	18.0
					(62.3	2.9	18.2)
IIIi	o-$OH-C_6H_4$	>300	63	$C_{16}H_{10}N_4O_2$	66.0	3.3	19.0
					(66.2	3.4	19.3)
IIIj	o-$NO_2-C_6H_4$	>300	58	$C_{16}H_9N_5O_3$	60.0	2.7	21.4
					(60.2	2.8	21.9)
IIIk	m-$NO_2-C_6H_4$	>300	60	$C_{16}H_9N_5O_3$	60.0	2.7	21.5
					(60.2	2.8	21.9)
IIIl	p-$N(CH_3)_2-C_6H_4$	>300	65	$C_{18}H_{15}N_5O$	67.9	4.6	21.9
					(68.1	4.7	22.1)

*The $M^{+\cdot}$ peaks appeared at *m/z* 290, 310, 288 and 308 for IIc, IIh, IIIc and IIIh, respectively.

(Ar=$p-CH_3-C_6H_4$). In this reaction the schiff base served only as a hydrogen acceptor. The samples of IIIc obtained by the above approaches were identical in all respects (m.m.p., co-TLC, co-IR and mass).

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol mull on a Perkin-Elmer 283 spectrometer, PMR spectra on a 100 MHz Varian spectrometer using TMS as internal standard, and mass spectra on a Varian MAT CH-7 instrument.

2,3-Dihydro-2-arylpyrimido[4,5-b][1,8]naphthyridin-4(1H)-ones (II): General procedure

A mixture of I (0.1 mol) and appropriate aromatic aldehyde (0.1 mol) was refluxed in gl. acetic

acid (25 ml) for 4 hr, cooled and poured onto crushed ice. The separated solid was filtered and recrystallised from dimethylformamide to give II (Table 1).

2-Arylpyrimido[4,5-b][1,8]naphthyridin-4(3H)-ones (III)

To a solution of II (0.01 mol) in gl. acetic acid (20 ml), was added nitrobenzene (10 ml), and the reaction mixture refluxed for 4 hr. The solid that separated on cooling was filtered, and washed with methanol in order to remove nitrobenzene. The compounds obtained by this procedure were recrystallized from acetic acid and are listed in Table 1.

Condensation of 2-amino-1,8-naphthyridine-3-carboxamide (I) with aldehydes in nitrobenzene-acetic acid: General procedure

A mixture of I (0.1 mol) and aromatic aldehyde (0.1 mol) was refluxed in gl. acetic acid (30 ml) containing nitrobenzene (20 ml) for 5 hr. The reaction mixture was subjected to steam-distillation to remove nitrobenzene. The non-volatile residue on purification and recrystallization gave III (Table 1).

Condensation of I with schiff bases in acetic acid: Formation of III—General procedure

2-Amino-1,8-naphthyridine-3-carboxamide (I; 0.1 mol) and schiff base (0.2 mol) were dissolved in a minimum quantity of gl. acetic acid and the mixture was refluxed for 4 hr, cooled and the separated solid (III) filtered and washed with ethanol.

The acetic acid filtrate on dilution with water gave the secondary amine (IV).

Oxidation of II with schiff bases in acetic acid: Formation of III—General procedure

To a solution of II (0.1 mol) in gl. acetic acid (20 ml) was added schiff base (0.1 mol), the reaction mixture refluxed for 4 hr and cooled. The solid (III) that separated was filtered and wahsed with ethanol. The acetic acid filtrate on dilution with water gave the secondary amine (IV).

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References

1 Gorecki D K J & Hawes E M, *J mednl Chem*, **20** (1977) 124.
2 Suzuki N, Kato M & Dohmori R, *Yakugaku Zasshi*, **99** (1979) 155; *Chem Abstr*, **91** (1979) 56865.
3 Suzuki N, Tanaka Y & Dohmori R, *Chem Pharm Bull*, **28** (1980) 235; *Chem Abstr*, **93** (1980) 71637.
4 Nigam S C, Saharia G S & Sharma H R, *J Indian chem Soc*, **60** (1983) 583.
5 Sen D, Bhowmik S & Sengupta P, *J Indian chem Soc*, **63** (1986) 420.
6 Hynes J B, Gratz R F & Aston W T, *J mednl Chem*, **15** (1972) 1332.
7 Kulkarni S E, Mane R A & Ingle D B, *Indian J Chem*, **25B** (1986) 452.
8 Mogilaiah K, Raghava Raju K & Sreenivasulu B, *Indian J Chem*, **20B** (1981) 821.
9 Mogilaiah K & Sreenivasulu B, *Indian J Chem*, **21B** (1982) 582.
10 Vijayender Reddy K, Mogilaiah K & Sreenivasulu B, *J Indian chem Soc*, **61** (1984) 888.
11 Reddy E J S, Reddy S M, Mogilaiah K & Sreenivasulu B, *Nat Acad Sci Lett*, **8** (1985) 19.
12 Rajendar Reddy K, Mogilaiah K & Sreenivasulu B, *J Indian chem Soc*, (in press).
13 Hawes E M & Wibberley D G, *J chem Soc (C)*, (1967) 1566.
14 Roe A & Montgmery J A, *J Am chem Soc*, **75** (1953) 911.

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Thiazolidinones, Azetidinones & Formazans of Quinazolinones†

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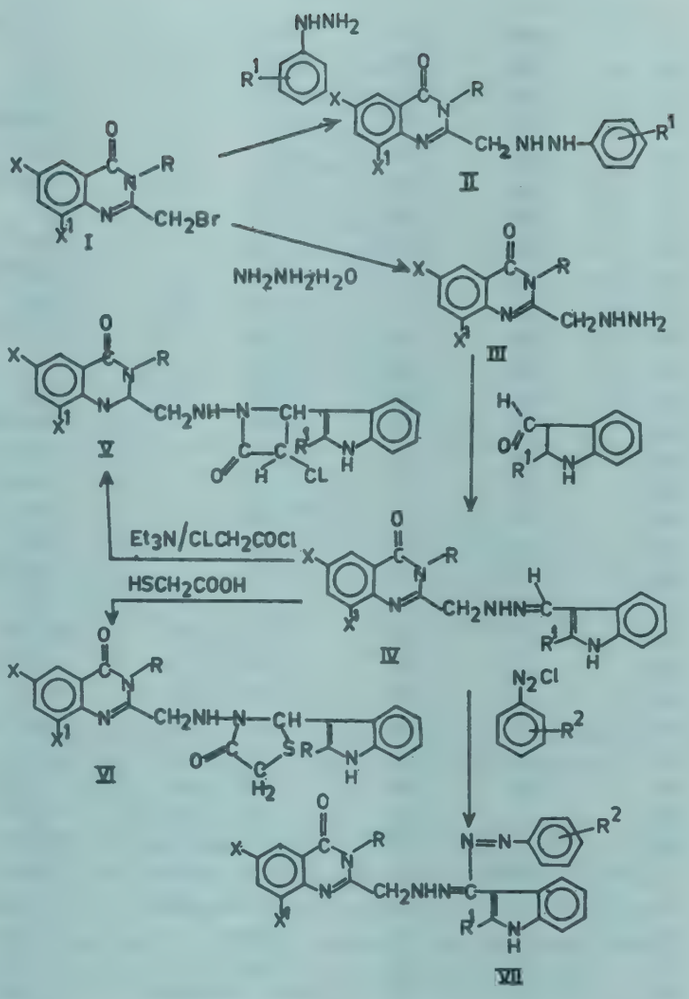
6,8-disubstituted 3-aryl-2-bromomethyl-4(3*H*)quinazolinones (I) react with hydrazine hydrate and substituted phenylhydrazines to yield 6,8-disubstituted 3-aryl-2-hydrazinomethyl-4(3*H*)-quinazolinone (III) and 6,8-disubstituted 3-aryl-2-(N^2-aryl-hydrazinomethyl)-4(3*H*)-quinazolinones (II) respectively. The compounds III on condensation with 3-arylindole-3-carboxaldehydes furnish 6,8-disubstituted 3-aryl-2-[N^2-(2-arylindol-3-ylmethylene)hydrazinomethyl]-4(3*H*)-quinazolinones (IV). These have been converted into the corresponding formazans (VII), thiazolidinones (VI) and azetidinones (V). All the structures have been elucidated by elemental analyses and PMR spectroscopy.

In continuation of our programme of developing newer quinazolone derivatives of biological importance we thought it proper to substitute the 2-position of quinazolinone with phenylhydrazine group, thereby linking the quinazolinone moiety by NHNH bridge. It is well documented that incorporation of an aryl group imparts significant biological activity in this moiety[1]. Therefore, we have also incorporated different heterocyclic moieties such as four-membered azetidines and five membered thiazolidinones at position-2.

6,8-Disubstituted 3-aryl-2-[N^2-(2-arylindol-3-ylmethylene)hydrazinomethyl]-4(3*H*)-quinazolinones (IV) were prepared by condensation of 2-substituted indole-3-carboxaldehydes with 6,8-disubstituted 3-aryl-2-hydrazinomethyl-4(3*H*)-quinazolinones (III) in abs. ethanol in the presence of gl. acetic acid. The structural assignments of III were based on elemental analyses and spectral data. Among the significant features of the PMR spectra of III was the appearance of methyleneamino proton (−CH=N−) downfield at δ 9.9 due to deshielding by the indole nucleus and the conjugated double bond system (−N=CH—O=).

Four membered β-lactam ring was introduced by the cycloaddition of monochloroacetyl chloride in the presence of triethylamine on the azomethane group of IV to yield 6-bromo-2-[3-chloro-2-oxo-4-(2-phenylindol-3-yl)azetidin-1-ylamino methyl]-3-(3-chloranilino)-4(3*H*)-quinazolinone (Vi; Table 1). Its structure was based on PMR spectrum which showed signals at δ 4.45 (*d*, 1H, azetidinyl CH, J=9 Hz), 6.7-8.5 (*m*, Ar-*H*), 6.25 (*d*, 1H, COCHCl, J=9 Hz); IR: 1710 (lactam C=O), 3300 cm^{-1} (NH).



The schiff bases IV on reaction with arenediazonium chlorides gave 6,8-disubstituted 3-aryl-2-[1-aryl-3-(2-arylindol-3-yl)-formazan-5-ylmethyl]-4(3*H*)-quinazolinones (VII; Table 2). The characteristic feature of this reaction is the replacement of methine proton of IV by the chlorine atom of the diazonium chloride. This was proved by the disappearance of the signal at δ 9.9 due to methine proton and the appearance of a more complex multiplet in the aromatic region due to additional aromatic protons [δ 6.6-8.8 (complex *m*, 24 H, 23 Ar − *H* and indole NH)].

Melting points are uncorrected. TLC was performed on silica gel G plates using benzene-methanol (8:2) as irrigant. PMR spectra in $CDCl_3$ or trifluoroacetic acid were recorded on an Em-360,

†Part of the work will be incorporated in Ph.D. thesis of D P Gupta.

Table 1 – Characterization Data of the Compounds II, V and VI

Compd	X	X^1	R	R^1	m.p. °C	Mol. formula	N (%) Found	N (%) Calc.
IIa	H	H	4-Cl	2,4-$(NO_2)_2$	192	$C_{21}H_{15}N_6O_5Cl$	18.0	18.0
IIb	H	H	4-Cl	H	124	$C_{21}H_{17}N_4OCl$	14.8	14.8
IIc	H	H	4-Cl	4-Cl	155	$C_{21}H_{16}N_4Cl_2$	14.1	14.1
IId	H	H	4-Cl	4-OCH_3	180	$C_{22}H_{19}N_4O_2Cl$	13.7	13.7
IIe	H	H	4-Cl	3-Cl	172	$C_{21}H_{16}N_4Cl_2$	14.1	14.1
IIf	Br	H	2-CH_3	2,4-$(NO_2)_2$	122	$C_{22}H_{17}N_6O_5Br$	16.0	16.0
IIg	Br	H	2-CH_3	H	143	$C_{22}H_{19}N_4OBr$	12.9	12.8
IIh	H	H	2-CH_3	4-Cl	132	$C_{22}H_{18}N_4OBrCl$	11.9	11.9
IIi	H	H	2-CH_3	4-OCH_3	212	$C_{23}H_{21}N_4O_2Br$	12.0	12.0
IIj	H	H	2-CH_3	3-Cl	181	$C_{22}H_{18}N_4OBrCl$	11.9	11.9
IIk	H	Br	2-CH_3	2,4-$(NO_2)_2$	165	$C_{22}H_{16}N_6O_5Br_2$	13.9	13.9
IIl	H	Br	2-CH_3	H	133	$C_{22}H_{18}N_4OBr_2$	10.8	10.8
IIm	H	Br	2-CH_3	4-Cl	202	$C_{22}H_{17}N_4OBr_2$	10.9	10.9
IIn	H	Br	2-CH_3	4-OCH_3	172	$C_{23}H_{20}N_4O_2Br$	10.2	10.2
IIo	H	Br	2-CH_3	3-Cl	146	$C_{22}H_{17}N_4OBr_2Cl$	10.2	10.2
IIp	H	H	2-CH_3	2,4-$(NO_2)_2$	162	$C_{22}H_{17}N_5O_5I$	14.6	14.6
IIq	H	H	2-CH_3	H	170	$C_{22}H_{19}N_4OI$	11.6	11.6
IIr	H	H	2-CH_3	4-Cl	145	$C_{22}H_{18}N_4OICl$	10.8	10.8
IIs	H	H	2-CH_3	4-OCH_3	186	$C_{23}H_{21}N_4O_2I$	10.9	10.9
IIt	H	H	2-CH_3	3-Cl	163	$C_{22}H_{18}N_4OICl$	10.8	10.8
Va	I	H	2-CH_3.C_6H_4	C_6H_5	190	$C_{33}H_{25}N_5ClIO_2$	10.2	10.2
Vb	I	H	2-CH_3.C_6H_4	4-CH_3.C_6H_4	205	$C_{34}H_{27}N_5O_2ICl$	10.0	10.0
Vc	Br	H	2-CH_3.C_6H_4	C_6H_5	182	$C_{33}H_{25}N_5O_2BrCl$	10.9	10.9
Vd	Br	H	2-CH_3.C_6H_4	4-CH_3.C_6H_4	171	$C_{34}H_{27}N_5O_2BrCl$	10.7	10.7
Ve	Br	Br	2-CH_3.C_6H_4	C_6H_5	185	$C_{33}H_{24}N_5O_2Br_2Cl$	9.7	9.7
Vf	Br	Br	2-CH_3.C_6H_4	4-CH_3.C_6H_4	151	$C_{34}H_{26}N_5O_2Br_2Cl$	9.5	9.5
Vg	I	H	4-Chloranilino	C_6H_5	180	$C_{32}H_{23}N_6O_2ICl_2$	11.6	11.6
Vh	I	H	4-Chloranilino	4-CH_3.C_6H_4	236	$C_{33}H_{25}N_6O_2ICl_2$	11.4	11.4
Vi	Br	H	3-Chloranilino	C_6H_5	192	$C_{31}H_{23}N_5O_2BrCl_2$	10.8	10.8
Vj	Br	H	3-Chloranilino	4-CH_3.C_6H_4	162	$C_{32}H_{25}N_5O_2BrCl_2$	10.6	10.5
Vk	H	H	Anilino	C_6H_5	195	$C_{31}H_{25}N_5O_2Cl$	13.0	13.0
Vl	H	H	Anilino	4-CH_3.C_6H_4	276	$C_{32}H_{27}N_6O_2Cl$	14.9	14.9
VIa	I	H	4-Chloranilino	C_6H_5	115	$C_{32}H_{24}N_5SCl\,I$	10.4	10.4
VIb	I	H	4-Chloranilino	4-CH_3.C_6H_4	125	$C_{33}H_{26}N_5SCl\,I$	10.1	10.1
VIc	Br	H	3-Chloranilino	C_6H_5	220	$C_{32}H_{24}N_5SCl\,Br$	11.1	11.1
VId	Br	H	3-Chloranilino	4-CH_3.C_6H_4	186	$C_{33}H_{26}N_5SCl\,Br$	10.9	10.9
VIe	I	H	2-CH_3.C_6H_4	C_6H_5	162	$C_{33}H_{26}N_4SI$	8.7	8.7
VIf	I	H	2-CH_3.C_6H_4	4-CH_3.C_6H_4	202	$C_{33}H_{26}N_4SI$	8.6	8.6
VIg	Br	H	2-CH_3.C_6H_4	C_6H_5	156	$C_{33}H_{26}N_4SBr$	9.4	9.4
VIh	Br	H	2-CH_3.C_6H_4	4-CH_3.C_6H_4	126	$C_{34}H_{26}N_4SBr$	9.2	9.2
VIi	Br	Br	2-CH_3.C_6H_4	C_6H_5	184	$C_{33}H_{25}N_4SBr_2$	8.3	8.3
VIj	Br	Br	2-CH_3.C_6H_4	4-CH_3.C_6H_4	103	$C_{34}H_{27}N_4SBr_2$	8.1	8.1
VIk	Br	H	4-Chloranilino	C_6H_5	124	$C_{32}H_{24}N_5SBrCl$	11.2	11.1
VIl	Br	H	4-Chloranilino	4-CH_3.C_6H_4	136	$C_{33}H_{26}N_5SBrCl$	10.9	10.9
VIm	H	H	Anilino	C_6H_5	205	$C_{32}H_{26}N_5S$	13.6	13.6
VIn	H	H	Anilino	4-CH_3.C_6H_4	172	$C_{33}H_{28}N_5S$	13.3	13.3

spectrometer using TMS as internal standard (chemical shifts in δ, ppm), and IR spectra in KBr on a Perkin-Elmer infracord 137 instrument (ν_{max} in cm^{-1}). 2-Substituted indole-3-carboxaldehydes were prepared following the method of Jerry *et al.*[2].

6,8-Disubstituted 3-aryl-2-(N²-arylhydrazinomethyl)-4-(3H)-quinazolinones (IIa-t; Table 1)

Compound I (0.19 g) was added to a solution of pyridine (5 ml) in ethanol (5 ml) and then substituted phenylhydrazine (0.02 mol) added to it. The reaction mixture was refluxed for 2 hr. The solid thus obtained was recrystallized from $CHCl_3$-pet. ether to give II, yield 80%; PMR ($CDCl_3$) of IIb: 6.85-8.05 (complex *m*, 13 H, Ar – *H*), 2.65 (*d*, 2H, CH_2), 4.85 (*brs*, 1H, NH attached to CH_2), 6.5 (*s*, 1H, NH attached to phenyl) (Found: N, 14.8; C, 69.6; N, 4.6. $C_{21}H_{17}N_4OCl$ requires N, 14.8; C, 66.8; N, 4.5%).

Table 2—Characterization Data of 6,8-Disubstituted 3-Aryl-2-[1-aryl-3-(2-arylindol-3-yl)formazan-5-ylmethyl]-4(3*H*)-quinazolinones (VII)

Compd	X	X^1	R	R^1	R^2	m.p. °C	Mol. formula	N (%)*	
								Found	Calc.
VIIa	I	H	4-Chloranilino	C_6H_5	H	132	$C_{36}H_{26}N_8OICl$	14.9	14.9
VIIb	I	H	4-Chloranilino	$4\text{-}CH_3.C_6H_4$	4-Cl	153	$C_{37}H_{17}N_8OICl_2$	14.7	14.7
VIIc	I	H	$2\text{-}CH_3.C_6H_4$	C_6H_5	H	122	$C_{37}H_{28}N_7OI$	13.7	13.7
VIId	I	H	$2\text{-}CH_3.C_6H_4$	$4\text{-}CH_3.C_6H_4$	4-Cl	140	$C_{38}H_{29}N_7OI$	13.4	13.4
VIIe	Br	H	$2\text{-}CH_3.C_6H_4$	C_6H_5	H	195	$C_{37}H_{28}N_7OBr$	14.7	14.7
VIIf	Br	H	$2\text{-}CH_3.C_6H_4$	$4\text{-}CH_3.C_6H_4$	4-Cl	152	$C_{38}H_{29}N_7OBrCl$	13.7	13.7
VIIg	Br	H	4-Chloranilino	C_6H_5	H	117	$C_{36}H_{26}N_8OBrCl$	15.9	15.9
VIIh	Br	H	4-Chloranilino	$4\text{-}CH_3.C_6H_4$	4-Cl	195	$C_{37}H_{27}N_8OBrCl_2$	14.9	14.9
VIIi	H	H	Anilino	C_6H_5	H	136	$C_{36}H_{28}N_8O$	19.0	19.0
VIIj	H	H	Anilino	$4\text{-}CH_3.C_6H_4$	4-Cl	142	$C_{37}H_{29}N_8OCl$	17.6	17.5
VIIk	Br	Br	$2\text{-}CH_3.C_6H_4$	C_6H_5	4-Cl	192	$C_{37}H_{26}N_7OBr_2Cl$	14.3	14.3
VIIl	Br	H	$2\text{-}CH_3.C_6H_4$	$4\text{-}CH_3.C_6H_4$	H	152	$C_{38}H_{28}N_7OBr_2$	12.9	12.9

6,8-Disubstituted 3-aryl/arylamino-2-[3-chloro-2-oxo-4-(2-arylindol-3-yl)azetidin-1-ylaminomethyl]4(3H)-quinazolinones (Va-1; Table 1)

To a solution of IV (0.02 mol) and triethylamine (0.02 mol) in dioxane (20 ml) was added chloroacetyl chloride (0.02 mol) dropwise with stirring in the cold. The reaction mixture was left at room temperature for 30 min and then refluxed for 3 hr. On cooling a solid separated out. It was removed by filtration and the filtrate triturated with ether-pet. ether (1:1) until it solidified. The solid was crystallized from a mixture of ethanol and water to give V. Compound Vi—PMR ($CDCl_3$): 6.7-8.5 (*m*, 18H, Ar—*H*), 6.25 (*d*, 1H, *J*=9 Hz, CH), 4.45 (*d*, 1H, *J*=9 Hz, lactam CH), 2.65 (*d*, 2H, $-CH_2-NH-$), 3.7 (*brs*, 1H, $-CH_2-NH-$), 6.55 (*s*, 1H, C_6H_5-NH-), 8.8 (*s*, 1H, indole NH), IR: 1710 (lactam C=O), 3300 (NH), 760 (C—Cl).

6,8-Disubstituted 3-aryl-2-[2-(2-arylindol-3-yl)thiazoldin-3-ylaminomethyl]-4(3H)-quinazolinones (VIa-n; Table 1)

To a solution of IV (0.02 mol) in dry benzene (30 ml) was added thioglycolic acid dropwise with stirring. The reaction mixture was left at room temperature for 4 hr whereupon a solid separated out. It was collected and crystallized from benzene-pet. ether. Compound VIm—PMR ($CDCl_3$): 6.6-8.4 (*m*, 18H, Ar—*H*), 2.64 (*d*, 2H, $-CH_2-NH-$), 2.80 (*s*, 2H, $-CH_2-S-$); 3.75 (*brs*, 1H, $-CH_2-NH-$), 6.50 (*s*, 1H, C_6H_5-NH-), 8.8 (*s*, 1H, indole NH), 6.3 (*s*, 1H, CH) (Found: N, 11.2; C, 69.6; H, 4.6. $C_{32}H_{24}N_5SBrCl$ requires N, 11.1; C, 69.5; H, 4.6%).

6,8-Disubstituted 3-aryl-2-[1-aryl-3-(2-arylindol-3-yl)formazan 5-ylmethyl]-4(3H)-quinazolinones (VIIa-1, Table 2)

Appropriate amine (0.02 mol) in gl. acetic acid (2 ml) and HCl (1.5 ml) was diazotized with sodium nitrite (0.2 g in 2 ml water) in the cold and the resultant diazonium solution added with stirring to IV (0.01 mol in pyridine) in the cold. The reaction mixture was left overnight at ambient temperature and poured into cold water (250 ml) with continuous stirring when a dark coloured solid separated out. It was filtered, washed repeatedly with water and recrystallized from methanol to give TLC pure VII. Compound VIIi—PMR ($CDCl_3$): 6.6-8.8 (complex *m*, 24H, 23 Ar-*H* and indole NH), 2.6 (*d*, 2H, $-CH_2-NH-$), 3.7 (*brs*, 1H, $-CH_2-NH-$) (Found: N, 19.0; C, 73.5; H, 4.8. $C_{36}H_{28}N_8O$ requires N, 19.0; C, 73.3; H, 4.7%).

References

1 Gujral M L, Saxena P N & Kohli R P, *Indian J Med Res*, **45** (1957) 207.

2 Jerry M, Edward M, Nicholas J, Micheal P C & Bryce D, *J mednl Chem*, **7** (1964) 738.

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Intramolecular Chemoselective Heterocyclisation of 4-Oxothiazolidin-5yl N-Aryldithiocarbamates to Fungitoxic 1,3-Dithiolo-, 1,3-Oxathiolo- & Thiazolo-thiazoles

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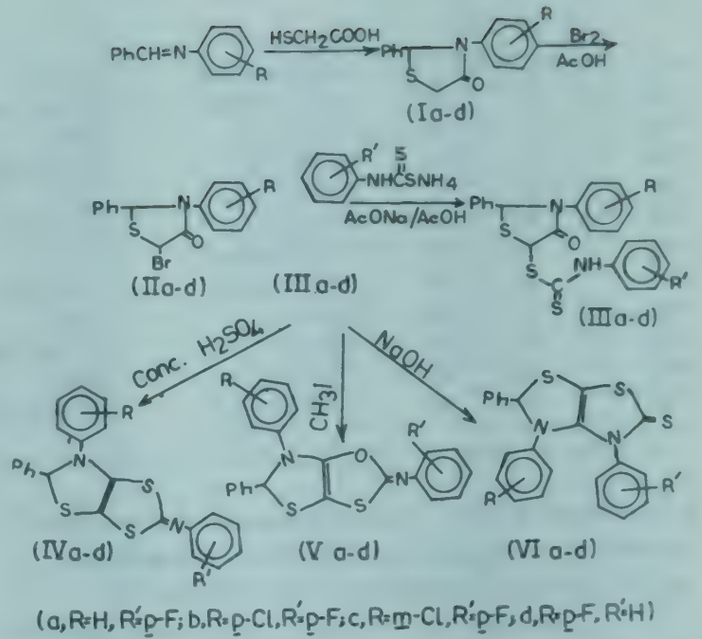
Substituted 1,3-dithiolo[4,5-*d*]thiazoles (IVa-d), 1,3-oxathiolo[5,4-*d*]thiazoles (Va-d) and thiazolo[4,5-*d*]thiazoles (VIa-d) have been synthesised by the intramolecular chemoselective heterocyclisation of 4-oxothiazolidin-5-yl N-aryldithiocarbamates (IIIa-d) with conc. H_2SO_4, CH_3I and NaOH, respectively. The compounds III-VI were compared with Dithane M-45 for their fungitoxicity against *A. niger* and *F. oxysporium*. Based on screening data, a possible structure-activity relationship has been deduced.

Some condensed ring systems incorporating thiazole nucleus fused with imidazole, 1,3,4-oxa(thia)diazoles or 1,2,4-triazole ring have been reported as potential fungicides[1-5]. In view of these reports and in continuation of our work[5-8] on fungitoxic condensed heterocycles, in the present investigation we have fused the biolabile thiazole nucleus with 1,3-dithiole, 1,3-oxathiole and thiazole rings to probe how far these combinations could enhance the fungitoxicity.

The reaction sequence leading to the formation of the title compounds has been outlined in Scheme 1. Chemoselectivity in the intramolecular cyclisation of the 4-thiazolidinon-5-yl N-aryldithiocarbamates (IIIa-d) leading to IV-VI may be rationalized on the basis of hard and soft acids and bases (HSAB). In the case of cyclisation of IIIa-d with conc. H_2SO_4, the protonation of the carbonyl oxygen leads to the corresponding IVa-d via intramolecular nucleophilic attack by thionic S of the dithiocarbamate function[9,10]. Methyl iodide, a soft Lewis acid, methylates the thionic S of the dithiocarbamate moiety of III followed by cyclisation to V with the elimination of methanethiol. The reaction of NaOH with III furnishes N,S-ambident anion, the terminal nitrogen of which attacks the carbonyl carbon to yield the corresponding VI[11].

The starting materials, 4-thiazolidinones (Ia-d) were prepared by the addition-condensation of



SCHEME 1

azomethines and mercaptoacetic acid[12]. These were brominated[13] with bromine and gl. acetic acid to afford IIa-d which on condensation with ammonium N-aryldithiocarbamates afforded IIIa-d, the synthons for the compounds IV-VI.

The synthesised compounds were characterised by their elemental analyses, and IR and PMR spectral data.

Fungicidal screening

The fungicidal activity of the compounds III-VI was evaluated against *Aspergillus niger* and *Fusarium oxysporium* by the usual agar-plate technique[14] at 1000, 100 and 10 ppm concentrations. Dithane M-45, a standard commercial fungicide, was also tested under similar conditions for comparison. The fungicidal screening results of the compounds III-VI are summarised in Table 1. Of these, the most active compounds IVb, VIb and VIc exhibited the activity equivalent to that of Dithane M-45 at 1000 ppm concentration. The screening data indicate that the presence of dithiocarbamate moiety[15,16] and compactness of the molecule[5,17] play key role in the fungitoxicity of these compounds.

M.ps were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer infrared spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on an EM-360L (60 MHz) NMR spectrometer using TMS as internal reference (chemical shifts in δ, ppm).

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Table 1—Fungicidal Screening Results of the Compounds III-VI

Compd	Average percentage inhibition against					
	A. niger at			*F. oxysporium* at		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IIIa	60	30	10	62	32	11
IIIb	76	43	21	73	42	23
IIIc	70	38	20	61	36	21
IIId	65	40	22	65	35	11
IVa	70	42	20	72	40	20
IVb	98	60	48	97	61	48
IVc	80	52	35	81	48	30
IVd	78	46	32	79	44	24
Va	66	40	16	64	38	13
Vb	89	56	39	87	54	38
Vc	76	44	30	87	50	27
Vd	73	42	28	75	40	18
VIa	82	50	38	81	51	30
VIb	99	65	51	98	62	50
VIc	99	62	50	97	60	49
VId	87	55	41	85	52	35
Dithane M-45 (a commercial fungicide)	100	81	67	100	85	68

2,3-*Diaryl*-4-*thiazolidinones* (Ia-d)

These compounds were prepared by the addition-condensation of azomethines and mercaptoacetic acid following the method of Astik *et al*[12]. The compounds Ia-c are already reported in literature[18]. Id: m.p. 118° (EtOH), yield 61% (Found: N, 4.8; S, 11.5. $C_{15}H_{12}FNOS$ requires N, 5.1; S, 11.7%); IR: 1700 ($\nu C=O$).

2,3-*Diaryl*-5-*bromo*-4-*thiazolidinones* (IIa-d)[13]

Bromination of the 4-thiazolidinones (Ia-d) with bromine in gl. acetic acid afforded the compounds IIa-d in 64-76% yield whichwere recrystallised from ethanol.

IIa: m.p. 105° (Found: C, 53.8; H, 3.4; N, 3.9. $C_{15}H_{12}BrNOS$ requires C, 53.9; H, 3.6; N, 4.2%); IR: 1705 ($\nu C=O$).

IIb: m.p. 93-94° (Found: C, 48.5; H, 2.9; N, 3.7. $C_{15}H_{11}BrClNOS$ requires C, 48.8; H, 3.0; N, 3.8%).

IIc: m.p. 100° (Found: C, 48.7; H, 2.8; N, 3.6. $C_{15}H_{11}BrClNOS$ requires C, 48.8; H, 3.0; N, 3.8%).

IId: m.p. 154-56° (Found: C, 50.8; H, 2.9; N, 3.8. $C_{15}H_{11}BrFNOS$ requires C, 51.1; H, 3.1; N, 4.0%); IR: 1710 ($\nu C=O$).

2,3-*Diaryl*-4-*oxothiazolidin*-5-*yl N*-*aryldithiocarbamates* (IIIa-d)

A mixture of IIa (16.7 g, 0.05 mol), ammonium N-phenyldithiocarbamate (9.3 g, 0.05 mol) and anhyd. sodium acetate was refluxed for 2 hr in abs. ethanol, cooled, poured into water and the precipitate filtered and recrysallised from ethanol to give IIIa, yield 15.4 g (70%), m.p. 116-18° (Found: N, 6.3; S, 21.9. $C_{22}H_{17}FN_2OS_3$ requires N, 6.4; S, 21.8%); IR: 1700 (C=O), 1505 (>N−CS−S)[19]; PMR: 5.48 (1H, *s*, C_5-H), 6.38 (1H, br *s*, C_2-H), 6.92-8.08 (14H, *m*, Ar−H), 9.38 (1H, br *s*, NH).

Similarly compounds IIIb-d were prepared in 68-72% yield, and recrystallised from ethanol. Their characterization data are as follows:

IIIb: m.p. 125-127° (Found: N, 6.0; S, 20.0. $C_{22}H_{16}ClFN_2OS_3$ requires N, 5.9; S, 20.3%); IR: 1705 (C=O), 1510 (>N−CS−S−); PMR: 550 (1H, *s*, C_5-H), 6.42 (1H, *br s*, C_2-H), 7.00-8.18 (13H, *m*, Ar−H), 9.40 (1H, br *s*, NH).

IIIc: m.p. 110-11° (Found: N, 5.7; S, 20.3. $C_{22}H_{16}ClFN_2OS_3$ requires N, 5.9; S, 20.3%.

IIId: m.p. 128-30° (Found: N, 6.1; S, 21.9. $C_{22}H_{17}FN_2OS_3$ requires N, 6.4; S, 21.8%).

5,6-*Diaryl*-2-*arylimino*-5,6-*dihydro*-2*H*-1,3-*dithiolo*-[4,5-*d*]*thiazoles* (IVa-d)

The dithiocarbamates IIIa-d (0.01 mol) were treated dropwise with conc. H_2SO_4 (5 ml). The mixture in each case was cooled and poured into ice-water after 30 min. On neutralisation with ammonia the desired product (IV) precipiated out which was recrystallised from ethanol, yield 83-87%.

IVa: m.p. 127-29° (Found: C, 62.3; H, 3.4; N, 6.4. $C_{22}H_{15}FN_2S_3$ requires C, 62.5; H, 3.6; N, 6.6%); IR: 1670 (exocyclic C=N); PMR: 6.36 (1H, br *s*, C_2-H), 7.00-8.04 (14H, *m*, Ar−*H*).

IVb: m.p. 158-160° (Found: C, 57.4; H, 2.9; N, 5.8. $C_{22}H_{14}ClFN_2S_3$ requires C, 57.6; H, 3.1; N, 6.1%); IR: 1675 (exocyclic C=N); PMR: 6.40 (1H, br *s*, C_2-H), 7.02-8.20 (13H, *m*, Ar−H).

IVc: m.p. 121-22° (Found: C, 57.8; H, 3.0; N, 6.0. $C_{22}H_{14}ClFN_2S_3$ requires C, 57.6; H, 3.1; N, 6.1%).

IVd: m.p. 182° (Found: C, 62.4; H,3.7; N, 6.4. $C_{22}H_{15}FN_2S_3$ requires C, 62.6; H, 3.6; N, 6.6%).

5,6-Diaryl-2-arylimino-5,6-dihydro-2H,1,3-oxathiolo-[5,4-d]thiazoles (Va-d)

An equimolar mixture of III and methyl iodide was refluxed for 6 hr in methanol, and excess of the solvent distilled off. The residue was treated with 5% NaOH and the product, thus obtained, washed with water and recrystallised from ethanol to furnish V in70-78% yield.

Va: m.p. 117-18° (Found: N, 7.0; S, 15.6. $C_{22}H_{15}FN_2OS_2$ requires N, 6.9; S, 15.8%).

Vb: m.p. 140° (Found: N, 6.2; S, 14.3. $C_{22}H_{14}ClFN_2OS_2$ requires N, 6.4; S, 14.5%); IR: 1680 (exocyclic C=N); PMR: 6.46 (1H, br *s*, C_2-H), 7.00-8.22 (13H, *m*, Ar−H).

Vc: m.p. 96° (Found: N, 6.1; S, 14.4. $C_{22}H_{14}ClFN_2OS_2$ requires N, 6.4; S, 14.5%); IR: 1675 (exocyclic C=N); PMR: 6.42 (1H, br *s*, C_2-H), 6.98-8.00 (13H, *m*, Ar−H).

Vd: m.p. 151-52° (Found: N, 7.1; S, 15.7. $C_{22}H_{15}FN_2OS_2$ requires N, 6.9; S, 15.8%).

3,4,5-Triaryl-2,3,4,5-tetrahydrothiazolo[4,5-d]-thiazole-2-thiones (VIa-d)

A solution of IIIa (4.4 g, 0.01 mol) in NaOH (aq. 4%, 33 ml) and ethanol (20 ml) was refluxed for 2 hr, cooled, poured into water and brought to *p*H 5-6 with 5N HCl. The precipitate was filtered and recrystallised from ethanol to give VIa, yield 3.2 g (76%), m.p. 141-42° (Found: N, 6.4; S, 22.6. $C_{22}H_{15}FN_2S_3$ requires N, 6.6; S, 22.7%). Similarly compounds VIb-d prepared in 78-80% yield and recrystallised from ethanol.

VIb: m.p. 171° (Found: N, 5.9; S, 21.3. $C_{22}H_{14}ClN_2S_3$ requires N, 6.1; S, 21.0%); IR: 1080 (C=S); PMR: 6.36 (1H, br *s*, C_2-H), 6.96-8.08 (13H, *m*, Ar−H).

VIc: m.p. 114-15° (Found: N, 6.3; S, 21.0. $C_{22}H_{14}ClFN_2S_3$ requires N, 6.1; S, 21.0%).

VId: m.p. 166-67° (Found: N, 6.5; S, 22.6. $C_{22}H_{15}FN_2S_3$ requires N, 6.6; S, 22.7%); IR 1075 (C=S); PMR: 6.30 (1H, br *s*, C_2-H), 7.00-8.10 (14H, *m*, Ar−H).

References

1 Krasovskii A N, Bogatyreva E I, Soroka I I, Kochergin P M & Grin N P, *Khim-Farm Zh*, **11** (1977) 51; *Chem Abstr*, **87** (1977) 102231q.

2 Ali A & Saksena R K, *J Indian chem Soc*, **58** (1981) 1117.

3 Paget C J & Wikel J H, *US Pat* 4,008,242 (1977); *Chem Abstr*, **86** (1977) 189959j.

4 Tsuzuki H, Koide H, Nishioka & Nakanishi I, *Aichiken Nogyo Sogo Shikenjo Kenkyu Koko KuA*, **7** (1975) 55; *Chem Abstr*, **85** (1976) 105199e.

5 Singh H, Yadav L D S & Chaudhary J P, *J Indian chem Soc*, **60** (1983) 768.

6 Singh H, Yadav L D S, Sharma K S & Singh A K, *Indian J Chem*, **22B** (1983) 1177.

7 Singh H, Yadav L D S & Sharma K S, *Agric biol Chem*, **47** (1983) 1017.

8 Singh H, Yadav L D S, Sharma K S & Chaudhary J P, *Acta chim hung*, **115** (1984) 377.

9 Ueno Y & Okawara M, *Synthesis*, (1979) 182.

10 Maffii G, Testa E & Ettore R, *Chem Abstr*, **53** (1959) 2211b.

11 Fostovskii I Ya & Vereshchagina N N, *Zhur Obshchel Khim*, **26** (1956) 2588; *Chem Abstr*, **51** (1957) 5055.

12 Astik R R, Joshi G B & Thaker K A, *J Indian chem Soc*, **52** (1975) 1071.

13 Gakhar H K, Chander S, H & Khurana H C, *J Indian chem Soc*, **52** (1975) 155.

14 Horsfall J G, *Bot Rev*, **11** (1945) 357.

15 van der Kerk G J M, *Chemical structure & fungicidal activity of dithiocarbamates*, (University Wisconsin Press, Madison) 1959, 280.

16 Thorn G D & Ludwig R A, *The dithiocarbamates & related compounds*, (Elsvier, Amsterdam, New York) 1962, 169 and 244.

17 Summer L A, *Tetrahedron*, **32** (1976) 615.

18 Surry R, *J Am chem Soc*, **69** (1947) 2911.

19 Ueno Y & Okawara M, *Chem Lett*, (1973) 863.

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Comaparvins from Sea Lily *Comaster multifida* (Müller)

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Comapavin (**1**), 6-mthoxycomaparvin 5-methyl ether (**2**) and 6-methoxycomaparvin (**3**) have been isolated from the sea lily, *Comaster multifida* (Müller) and characterised by comparison of their melting points and IR, UV and PMR data with those reported in literature.

Several angular naphthopyrone pigments designated as comaparvins have been isolated from the sea lily *Comanthus paricirrus timorensis*[1]. We have analyzed extracts of the sea lily *Comaster multifida* (Müller) collected near Moen Island, Truk Lagoon, Eastern Caroline Islands, and isolated approximately equal amounts of the known pigments comaparvin (**1**) and 6-methoxycomaparvin 5-methyl ether (**2**), and 6-methoxycomaparvin (**3**). Identifications were made by comparison of melting points and IR, UV and PMR data with literature values.

In their original report on **1** and **2**, Smith and Sutherland[1] noted that if the crinoids were immersed in acetone immediately after collection, only sulfate esters of the phenols were isolated, whereas the sulfate-free phenols were extracted from animals which had been allowed to autolyze. In our case some time elapsed between collection and immersion in ethanol and accordingly the free phenol metabolites were isolated.

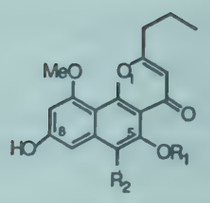
The general experimental procedures, adopted by Gunasekera and Schmitz[2] were used.

Animal collection

C. multifida was collected during September, 1979 near the airport runway at Moen Island, Eastern Caroline Islands, at −6 M and preserved in ethyl alcohol. A reference specimen (80-GS-59) is on deposit at the University of Oklahoma.

Extraction and isolation

Sea lillies (105 g dry wt after extraction) preserved in ethanol were filtered and extracted with 1:1 MeOH − $CHCl_3$ (3 × 1 litres) and the concentrated extracts were partitioned between $CHCl_3$ and H_2O. A portion (2 g) of the $CHCl_3$ extracts (4.8 g) was chromatographed over Sephadex LH-20 using 1:1 $CHCl_3$ − MeOH to give two groups of fractions containing yellow pigments according to TLC. From the early fractions of the chromatography, pure 6-methoxycomaparvin 5-methyl ether (**2**) (2 mg) was obtained by repeated chromatography over silica gel and a final separation using HPLC with a C-18 reversed phase column using 10% aqueous methanol as eluant; yellow crystals (MeOH − H_2O), m.p. 222-25°C [lit.[1] m.p. 221-22° (d)].



1 R_1, R_2 = H
2 R_1 = Me; R_2 = OMe
3 R_1 = H; R_2 = OMe

Preparative layer chromatography of one of the early fractions yielded **2** and **3**.

From the later LH-20 chromatography fractions comaparvin (**1**) was obtained by preparative layer chromatography (silica gel; 5% MeOH in $CHCl_3$); 2 mg, yellow needles (aq. MeOH), m.p. 232-33° (d) [lit.[1] m.p. 232-33°(d)].

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References

1 Smith I R & Sutherland M D, *Aust J Chem*, **24** (1971) 1487.

2 Gunasekera S P & Schmitz F J, *J org Chem*, **48** (1983) 885.

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Synthesis & Biological Activity of 3-Pentadecylaryloxyacetic Acids, Their Hydrazides & Cyclic Derivatives: Oxadiazoles & Pyrroles

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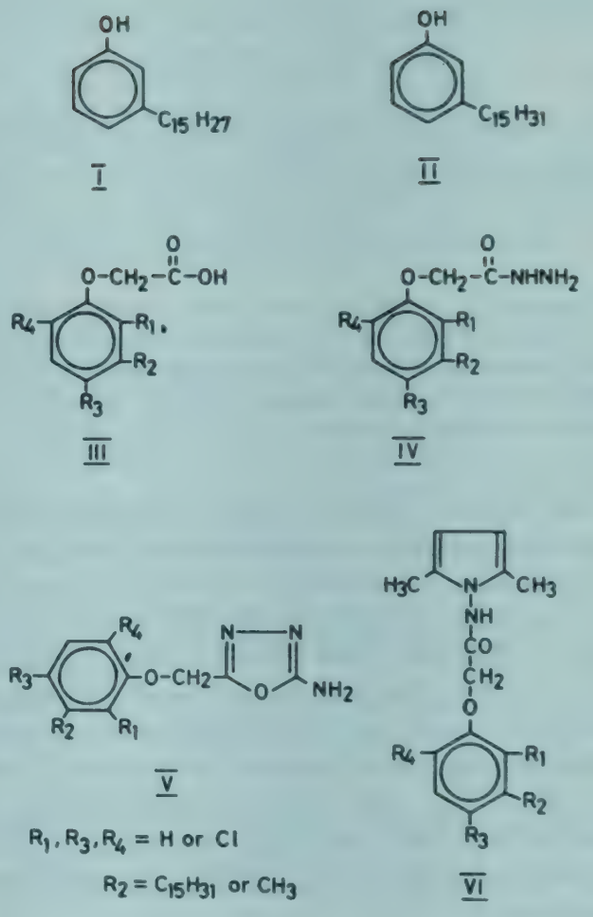
Several 3-pentadecylaryloxyacetic acids (III), their hydrazides (IV), 2-amino-5-(3′-pentadecylaryloxymethyl)-1,3,4-oxadiazoles (V) and 1-(3′-pentadecylaryloxyacetamido)-2,5-dimethylpyrroles (VI) have been synthesised and evaluated for their biological activity. Some of the compounds exhibit strong antiinflammatory action in experimental animals. Presence of a long alkyl chain ($C_{15}H_{31}$) renders the compounds to be less toxic.



The unique feature of cardanol (I), a *meta*-substituted long chain alkylphenol containing an average of two double bonds in the alkyl side chain and obtained by distillation of cashewnut shell liquid (CNSL) under reduced pressure, is that on catalytic hydrogenation it gives 3-pentadecylphenol (3-PDP, II) which offers a great chemical maneuverability for the synthesis of a variety of compounds.

In view of the fact that *meta*-alkylphenols are not easy to synthesise and the availability of CNSL in abundance, it was considered of interest to synthesise compounds incorporating a 3-PDP moiety and study their biological activity. The biological activity shown by various aryloxyacetic acids[1], hydrazides[2], 1,3,4-oxadiazoles[3] and pyrroles[4] also prompted us to synthesise 3-pentadecylaryloxyacetic acids (IIIb,d,e), their hydrazides (IVb,d,e), 2-amino-5-(3′-pentadecylaryloxymethyl)-1,3,4-oxadiazoles (Vb,d,e) and 1-(3′-pentadecylaryloxyacetamido)-2,5-dimethylpyrroles (VIb,d,e) and also their methyl analogues (IIIa,c, IVa,c, Va,c and VIa,c).

3-Pentadecylaryloxyacetic acids (III) were prepared by reacting the corresponding 3-pentadecylphenols with monochloroacetic acid in the presence of alkali and ethanol. These acids (III) were converted into hydrazides (IV) via their methyl esters. The oxadiazoles (V) and pyrroles (VI) were prepared by condensing IV with cyanogen bromide and acetonylacetone respectively according to the procedures given in experimental. The structural assignments of all the compounds prepared are based on elemental analyses and spectral data (IR, PMR and mass). Their characterization data are given in Table 1.

3-PDP was obtained by catalytic hydrogenation of cardanol(I)[5]. 4-Chloro-3-pentadecylphenol[6] was prepared by chlorination of 3-PDP employing sulphuryl chloride. 2,4,6-Trichloro-3-PDP was prepared for the first time by gaseous chlorination of 3-PDP. Its structure was based on PMR data. The PMR signal due to aromatic proton appeared at δ 7.3 both in trichloro-3-PDP and its acetyl derivative clearly indicating the chlorination product to be 2,4,6-trichloro-3-PDP and not the 4,5,6-trichloro isomer because the signal due to *ortho*-proton of the acetyl derivative of 4,5,6-trichloro-3-PDP would have been deshielded due to close proximity to O-acetyl group.

Biological activity

Toxicity (LD_{50}), antiinflammatory, hypotensive and motor activities of the compounds III-VI were determined by literature methods[7-9]. All the compounds bearing a 3-PDP moiety were devoid of toxicity as shown by their LD_{50} values which were more than 800 mg/kg oral (i.p. mice) while the corresponding methyl substituted derivatives pos-

Table 1—Characterization Data of 3-Pentadecylaryloxyacetic Acids (III), Their hydrazides (IV), 1,3,4-Oxadiazoles (V) and Pyrroles (VI)

Compd	R_1	R_2	R_3	R_4	Yield (%)	m.p. °C (lit.)	Mol. formula	Found (Calc) (%)*	
								C	H
IIIa	H	CH_3	H	H	91	101-2 (101-2)[10]	—	—	—
IIIb	H	$C_{15}H_{31}$	H	H	77	108-9 (109-10)[6]	—	—	—
IIIc	H	CH_3	Cl	H	80	178 (177-78)[11]	—	—	—
IIId	H	$C_{15}H_{31}$	Cl	H	68	99-100	$C_{23}H_{37}ClO_3$	69.8 (69.6	9.2 9.4)
IIIe	Cl	$C_{15}H_{31}$	Cl	Cl	58	115-16	$C_{23}H_{35}Cl_3O_3$	59.6 (59.3	7.7 7.6)
IVa	H	CH_3	H	H	96	108-9 (110)[12]	—	—	—
IVb	H	$C_{15}H_{31}$	H	H	96	94	$C_{23}H_{40}N_2O_2$	73.5 (73.5	10.7 10.7)
IVc	H	CH_3	Cl	H	96	178	$C_9H_{11}ClN_2O_2$	50.3 (50.4	5.3 5.2)
IVd	H	$C_{15}H_{31}$	Cl	H	92	96	$C_{22}H_{39}ClN_2O_2$	67.0 (67.2	9.7 9.6)
IVe	Cl	$C_{15}H_{31}$	Cl	Cl	85	77-79	$C_{23}H_{37}Cl_3N_2O_2$	57.8 (57.7	7.9 7.8)
Va	H	CH_3	H	H	99	136-37 (137-38)[13]	—	—	—
Vb	H	$C_{15}H_{31}$	H	H	96	125	$C_{24}H_{39}N_3O_2$	72.0 (71.8	9.9 9.8)
Vc	H	CH_3	Cl	H	98	167	$C_{10}H_{10}ClN_3O_2$	50.0 (50.1	4.1 4.2)
Vd	H	$C_{15}H_{31}$	Cl	H	98	121-22	$C_{24}H_{38}ClN_3O_2$	66.3 (66.1	8.9 8.8)
Ve	Cl	$C_{15}H_{31}$	Cl	Cl	97	115-17	$C_{24}H_{36}Cl_3N_3O_2$	57.3 (57.1	7.3 7.2)
VIa	H	CH_3	H	H	97	168-69	$C_{15}H_{18}N_2O_2$	69.9 (69.7	7.2 7.0)
VIb	H	$C_{15}H_{31}$	H	H	95	83-84	$C_{29}H_{46}N_2O_2$	76.8 (76.6	10.3 10.2)
VIc	H	CH_3	Cl	H	97	215	$C_{15}H_{17}ClN_2O_2$	61.8 (61.6	6.2 5.9)
VId	H	$C_{15}H_{31}$	Cl	H	92	115-16	$C_{29}H_{45}ClN_2O_2$	71.1 (71.2	9.0 9.2)
VIe	Cl	$C_{15}H_{31}$	Cl	Cl	86	70-71	$C_{29}H_{43}Cl_3N_2O_2$	62.2 (62.4	7.7 7.8)

sessed LD_{50} values ranging from 400 to 700 mg/kg (i.p. mice). Compounds IIId, IVe, Ve, VIb and VIe which bear a 3-PDP moiety showed significant antiinflammatory activity (34, 38, 37, 34 and 33% respectively) in rats while phenylbutazone at the same dose (100 mg/kg, p.o.) produced 33% inhibition of carrageenin-induced inflammation. Spontaneous motor activity in mice was studied using an actophotometer. While the oxadiazoles Vb and Ve decreased the motor activity to the extent of 53 and 50% respectively, the hydrazide IVc increased it to 52%. The acid IIId produced gradual and sustained fall in blood pressure to 25%. None of the compounds exhibited remarkable hypotensive action to warrant further investigation. The results are given in Table 2.

Melting points were taken in open capillaries on a Buchi 510 melting point apparatus and are uncorrected. Homogeneity of the compounds was checked by TLC on silica gel G using chloroform-methanol (9:1) as irrigant. IR spectra were recorded on a Perkin-Elmer 222 spectrophotometer (ν_{max} cm^{-1}), PMR spectra on a Varian A60A spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a Hitachi RMU6L mass spectrometer at 70 eV.

Table 2—Biological Screening Results of the Compounds III, IV, V and VI

Compd	LD_{50} (mg/kg i.p. mice)	Percentage Motor activity* at 1/10 of LD_{50}	Antiinflammatory action at 1/10 of LD_{50} (% inhibition)
IIIa	700	40↓	15
IIIb	>800	20↓	24
IIIc	700	21↓	43
IIId	>800	15↓	34
IIIe	>800	15↓	13
IVa	400	↑12	17
IVb	>800	↑ 7	15
IVc	>800	↑52	24
IVd	>800	↑ 2	7
IVe	>800	23↓	38
Va	600	↑ 7	9
Vb	>800	53↓	28
Vc	700	37↓	24
Vd	>800	41↓	9
Ve	>800	50↓	37
VIa	700	22↓	14
VIb	>800	14↓	34
VIc	700	11↓	17
VId	>800	↑ 6	28
VIe	>800	29↓	33

*↓indicates decrease; ↑indicates increase

2,4,6-*Trichloro*-3-*pentadecylphenol*

To a solution of 3-PDP (II; 100 g) in pet. ether (60-80°; 500 ml) was added iodine (0.2 g), the mixture cooled in an ice-bath at 10-11° and dry chlorine gas passed through it slowly at the rate of 10-12 bubbles per min for 30 min. The ice-bath was removed and chlorination continued at 30° for antoher 30 min. When 37 g of chlorine was absorbed, the chlorination was stopped and the mixture taken in a separating funnel. Excess of chlorine and hydrogen chloride were removed by washing with water. The ether layer was dried (anhyd. sodium sulphate) and solvent stripped off to give the title compound as a light yellow solid, m.p. 54-56°, yield 128.6 g (96%) (Found: C, 61.7; H, 7.9. $C_{21}H_{33}Cl_3O$ requires C, 61.8; H, 8.2%); PMR(CCl_4): 7.30 (*s*, 1H, aromatic C_5-H), 5.75 (*br*, 1H, OH), 2.70-2.83 (*br*, 2H, $Ar-CH_2$), 1.25 [*s*, 26H, $(CH_2)_{13}$] and 0.80-0.95 (*t*, 3H, CH_3).

2,4,6-*Trichloro*-3-*pentadecylphenoxyacetic acid* (IIIe)

To a solution of 2,4,6-trichloro-3-PDP (40 g) in ethanol (150 ml) was added 40% aq. potassium hydroxide (35 ml). 20% alcoholic monochloroacetic acid (50 ml) was added in portions and the reactions mixture refluxed for 4 hr, poured over crushed ice and acidified. The crude product was filtered, washed with water and recrystallised from *n*-hexane to give IIIe (Table 1); PMR($CDCl_3$): 11.20 (*s*, 1H, COOH), 7.30 (*s*, 1H, aromatic C_5-H), 4.62 (*s*, 2H, OCH_2), 2.50-2.70 (*br*, 2H, $Ar-CH_2$), 1.20 [*s*, 26H, $(CH_2)_{13}$] and 0.70-0.85 (*t*, 3H, CH_3).

Compounds IIIa,b,c and d (Table 1) were prepared in a similar manner.

3-*Pentadecylphenoxyacetic acid hydrazide* (IVb)

A mixture of methyl 3-pentadecylphenoxyacetate (40 g), ethanol (250 ml) and hydrazine hydrate (30 ml) was refluxed on a steam-bath for 5 hr, concentrated and poured over crushed ice. The crude product was filtered, washed with cold water and recrystallised from ethanol to give IVb (Table 1); IR(KBr): 3320 (NH_2), 3200 (NH), 2920 and 2850 (CH_2 groups of $C_{15}H_{31}$), 1660 (CO), 1580 (aromatic) and 1245 (ether linkage); PMR($CDCl_3$): 6.5-7.1 (*m*, 5H, $Ar-H$ and $N-H$), 3.6-3.8 (*br*, 2H, NH_2), 4.6 (*s*, 2H, OCH_2), 2.7-2.8 (*br*, 2H, $Ar-CH_2$), 1.25 [*s*, 26H, $(CH_2)_{13}$] and 0.80-0.95 (*t*, 3H, CH_3).

Compounds IVa,c,d and e (Table 1) were synthesised in a similar way.

2-*Amino*-5-(3′-*pentadecylphenoxymethyl*)-1,3,4-*oxadiazole* (Vb)

To a solution of IVb (9.4 g; 0.025 mol) in a mixture of methanol (50 ml) and dimethylformamide (30 ml), was added freshly prepared cyanogen bromide and the reaction mixture warmed when it became a clear solution. After cooling for 1 hr at room temperature, the crude product was precipitated by the addition of aq. potassium bicarbonate solution. It was filtered, washed with water and crystallised from ethanol to give Vb (Table 1); IR(KBr): 3280, 3100 (NH_2), 2920 and 2850 (CH_2 groups of $C_{15}H_{31}$), 1640 (C=N) and 1250 (ether linkage); MS: *m/z* 401 ($M^{+\cdot}$).

Compounds Va,c,d and e (Table 1) were prepared in a similar manner.

1-(3′-*Pentadecylphenoxyacetamido*)-2,5-*dimethylpyrrole* (VIb)

A mixture of IVb (18.8 g; 0.05 mol), acetonylacetone (6.8 g; 0.06 mol), ethanol (150 ml) and acetic acid (20 ml) was refluxed for 3 hr, concentrated and poured into ice water. The product thus obtained was filtered, washed with water and crystallised from ethanol to give VIb (Table 1); IR(KBr): 3200 (NH), 1680 (CO), 1580 (C=C), 1250 (ether), 2920 and 2845 (CH_2 groups of $C_{15}H_{31}$); MS: *m/z* 454 ($M^{+\cdot}$), 361 ($M^+ - C_6H_7N$), 317 ($M^+ - C_7H_9N_2O$), 304 ($M^+ - C_8H_{10}N_2O$), 303 ($M^+ - C_8H_{11}N_2O$), 287 ($M^+ - C_8H_{11}N_2O_2$),

137 ($M^+ - C_{22}H_{37}O$), 110 ($M^+ - C_{23}H_{36}O_2$), 109 ($M^+ - C_{23}H_{37}O_2$), 108 ($M^+ - C_{23}H_{38}O_2$), 95 ($M^+ - C_{23}H_{37}NO_2$) and 94 ($M^+ - C_{23}H_{38}NO_2$).

Compounds VIa,c,d and e (Table 1) were prepared in a similar way.

References

1 Syntex Corporation, *Brit Pat*, 1216882 (1970); *Chem Abstr*, **74** (1971) 125268.

2 Kametani T, *Jap Pat*, 4059 (1967); *Chem Abstr*, **67** (1967) 81972.

3 Franklin W S & Loren M L, *J heterocycl Chem*, **6** (1969) 707.

4 Lotti B & Vezzosi O, *Farmaco Ed Sci*, **27** (1972) 317; *Chem Abstr*, **77** (1972) 48127.

5 Madhusudhan V, Ramiah M S, Naidu N B & Sivasamban M A, *Indian J Technol*, **11** (1973) 347.

6 Sethi S C, Subba Rao B C, Kulkarni S B & Katti S S, *Indian J Technol*, **1** (1963) 354.

7 Sheth U K, Dadkar N K & Kamat U G, *Selected topics in experimental pharmacology* (M B Kothari, Bombay) 1972, 124.

8 Harris L S & Uhle F C, *J pharmacol exptl Therap*, **132** (1961) 251.

9 Winter C A, Riseley E A & Nuss G W, *Proc Soc exptl Biol Med*, **111** (1962) 544.

10 Fawcett C H, Osborne D J & Walker R D, *Ann appl Biol*, **40** (1953) 231.

11 Synerholm M E & Zimmerman P W, *Contrib Boyce Thompson Inst*, **14** (1945) 91; *Chem Abstr*, **40** (1946) 1473.

12 Conti L, *Boll Sci Fac Chim Ind*, **22** (1964) 13; *Chem Abstr*, **61** (1964) 4253.

13 Gehlen H & Uteg K H, *Arch Pharm*, **301** (1968) 911.

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Synthesis of 11,12-Bis(aryl-amido/imido-alkyl)-12*H*-benzo[*b*]phenothiazines as Potential Anthelmintics

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Condensation of N-(hydroxyalkyl)aryl-amides/imides (I) with β-naphthol gives 1-(aryl-amido/imido-alkyl)-2-naphthols (II) which on reaction with aniline in the presence of Zn dust afford 1-(aryl-amido/imido-alkyl)-N-aryl-2-naphthylamines (III). Heating of III in the presence of sulphur and iodine furnishes 11-(aryl-amido/imido-alkyl)-12*H*-benzo[*b*]phenothiazines (IV). Condensation of IV with N-hydroxyalkyl-amides/imides affords 11,12-bis(aryl-amido/imido-alkyl)-12*H*-benzo[*b*]phenothiazines (V). Some of the compounds show anthelmintic activity ranging from 5 to 95%.

Evidences gathered so far indicate that the anthelmintic activity of phenothiazines is due to either phenothiazine δ-oxide or its metabolic products formed *in situ*[1,2]. These products paralyse the muscular system and interfere with the vital redox system[3–5], thereby destroying the parasite. The phenothiazines exert their anthelmintic action by coming in direct contact with the cuticle of parasite. In view of these observations it was thought desirable to synthesize some new phenothiazine derivatives for better therapeutic results. The present note describes the synthesis and anthelmintic activity of the title compounds (V; Table 1).

These compounds were prepared by the condensation of 11-(aryl-amido/imido-alkyl)-12*H*-benzo[*b*]phenothiazines (IV) with amido alcohols such as N-(hydroxymethyl)-and N-(hydroxyethyl)-phthalimides, N-(hydroxymethyl)benzamide and N-(hydroxymethyl)nicotinamide. The reaction sequence leading to the formation of V is shown in Scheme 1. All the new compounds were screened for their anthelmintic activity *in vivo* against *Ancylostoma ceylanicum* in hamsters and *Nippostrongylus brasiliensis* in rats. The compounds were found to possess significant activity against *A. ceylanicum* and *N. brasiliensis*.

Pharmacological activity

All the compounds (V) were tested for their antihookworm activity against *N. brasiliensis* by incubating the male rats with 500 infected larvae of *N. brasiliensis*. On the 9th day of infection, samples of faeces from rats were taken for experiment. The infected rats were divided in groups of three animals and starved for 24 hr. A group of 3 animals was left untreated as control. On the 9th day the test compounds were administered to the rats except the control group at a dose of 250 mg/kg × 3. The rats including the control were starved on the 10th day. They were sacrificed on the next day and worm loads of both the treated and control rats were compared.

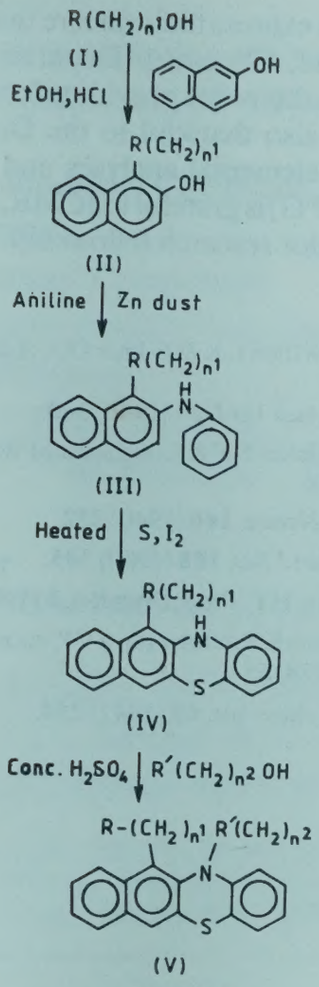
Hamsters of either sex weighing 40-60 g were infected orally with 603rd stage of larvae of *A. ceylani-*

Table 1—Characterization Data of 11,12-Bis(aryl-amido/imido-alkyl)-12*H*-benzo[*b*]-phenothiazines (V)

Compd	R	n^1	R^1	n^2	m.p. °C	Mol. formula	Found(%) (Calc.)		
							C	H	N
V_1	Phthalimido	1	Benzamido	1	120	$C_{33}H_{23}N_3O_3S$	73.2(73.2)	4.2(4.3)	7.7(7.8)
V_2	Phthalimido	1	Nicotinamido	1	100	$C_{32}H_{22}N_4O_3S$	70.8(70.8)	4.0(4.1)	10.3(10.3)
V_3	Phthalimido	1	Phthalimido	2	105	$C_{35}H_{23}N_3O_4S$	72.2(72.3)	3.9(4.0)	7.2(7.2)
V_4^*	Benzamido	1	Phthalimido	1	180	$C_{33}H_{23}N_3O_3S$	73.1(73.2)	4.2(4.3)	7.8(7.8)
V_5^*	Benzamido	1	Phthalimido	2	140	$C_{34}H_{25}N_3O_3S$	73.4(73.5)	4.4(4.5)	7.5(7.6)
V_6^*	Benzamido	1	Nicotinamido	1	165	$C_{31}H_{24}N_4O_2S$	69.9(69.9)	4.6(4.5)	10.5(10.5)
V_7^*	Nicotinamido	1	Phthalimido	1	115	$C_{32}H_{22}N_4O_3S$	70.8(70.8)	4.0(4.1)	10.3(10.3)
V_8	Nicotinamido	1	Benzamido	1	130	$C_{31}H_{24}N_4O_2S$	70.0(69.9)	4.4(4.5)	10.4(10.5)
V_9	Nicotinamido	1	Phthalimido	2	110	$C_{33}H_{24}N_4O_3S$	71.2(71.2)	4.3(4.3)	10.0(10.1)
V_{10}	Phthalimido	2	Phthalimido	1	170	$C_{35}H_{23}N_3O_4S$	72.2(72.3)	3.9(4.0)	7.2(7.2)
V_{11}	Phthalimido	2	Benzamido	1	136	$C_{34}H_{25}N_3O_3S$	73.5(73.5)	4.5(4.5)	7.4(7.6)
V_{12}	Phthalimido	2	Nicotinamido	1	210	$C_{33}H_{24}N_4O_3S$	71.2(71.2)	4.3(4.3)	10.0(10.1)

*The compounds showed IR(KBr) absorption bands at 3400 ± 10 (N-H), 1620 ± 10 (N-H bending), 1710 (C = O) and 3300 (aromatic C-H).

†PMR(CDCl$_3$ + DMSO-d_6): 7.3-7.9 (*m*, 17H, Ar-*H*), 8.7 (*t*, 1H, N-H), 4.9 (*d*, 2H, NHCH_2) and 2.3 (*s*, 2H, N-CH_2).



SCHEME 1

cum on day 17-20 post inoculation. Hamsters found positive were treated with test compounds and anti-hookworm drug[6] in groups of 3-5 animals in each dose schedule. The efficacy was expressed in terms of absolute clearance of host and present worm reduction. The percent activity was calculated by the following formula - Percent anthelmintic activity

$$= \frac{N\text{-}n}{N} \times 100$$

Where N = number of worms count in control and n = number of worms count in treated animals.

All the phenothiazine derivatives exhibited varying degree of anthelmintic activity against *A. ceylanicum*. It was found that the phenothiazine derivative V_1 with phthalimido and benzamido groups at positions 11 and 12 respectively showed the maximum activity (95%, Table 2) against *A. ceylanicum*. It is very interesting to observe that even a minor change in the molecular configuration of these compounds profoundly influences their activity. Thus, compound V_{ii} with a methylphthalimido and benzamido groups at position 11 and 12 respectively was completely inactive against *A. ceylanicum*. Furthermore the compound V_{12} having phthalimido and nicotinamido groups at position 11 and 12 respectively, was the most active compound against *N. brasiliensis* (Table 2). Rest of the compounds exhibited mild activity against *N. brasiliensis*.

Table 2—Anthelmintic Activity of 11,12-Bis-(aryl-amido/imido alkyl)-12 *H*-benzo[*b*]phenothiazines (V) against *A. ceylanicum* and *N. brasiliensis* at 250 mg/kg Dose

Compd	Activity (%) against	
	A. ceylanicum	*N. brasiliensis*
V_1	95	16
V_2	75	21
V_3	59	5
V_4	21	Inactive
V_5	10	-do-
V_6	17	-do-
V_7	23	-do-
V_8	5	-do-
V_9	42	-do-
V_{10}	19	25
V_{11}	Inactive	28
V_{12}	-do-	46

Melting points were determined in open capillaries using H_2SO_4 bath and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in a mixture of DMSO-d_6 and $CDCl_3$ on a Varian $A_{60}D$ instrument using TMS as internal standard (chemical shift in δ, ppm).

N-(Hydroxyalkyl)aryl-amides/imides (I)

The method of Buc[7] was followed for the preparation of N-(hydroxymethyl)phthalimide),N-(hydroxyethyl)phthalimide, N-(hydroxymethyl)benzamide and N-(hydroxymethyl)nicotinamide.

1-(*Aryl-amido/imido-alkyl*)-2-*naphthol* (II)

An equimolar (0.01 mol) mixture of 1 and 2-naphthol in ethanol (20 ml) with a few drops of conc. HCl was refluxed for 4 hr on a steam-bath. The solvent was distilled off and the solid product washed repeatedly with water and recrystallised from ethanol to get II (yield 50-65%).

1-(*Aryl-amido/imido-alkyl*)-*N-aryl*-2-*naphthylamines* (III)

A mixture of 1-(aryl-amido/imido-alkyl)-2-naphthol (II; 0.01 mol) and primary aromatic amine (0.015 mol) in abs. ethanol (20 ml) was heated under reflux in the presence of anhydrous $ZnCl_2$ (0.2 g) for 5 hr, cooled, and the separated crude mass filtered, washed repeatedly with cold water, dried and recrystallised from ethanol to get III (yield 50-60%).

11-(*Aryl-amido/imido-alkyl*)-12 *H-benzo[b]phenothiazines* (IV)

A mixture of III (0.015 mol), sulphur (0.1 mol) and iodine (0.15 g) was rapidly heated at 215-220°C in an oil-bath and kept at this temperature for 1 hr. The hot melt was rapidly poured into a mortar, cooled and crushed to the powder. It was heated with animal charcoal and recrystallised from ethanol to get IV (yield-45-55%).

11,12-*Bis(aryl-amido/imido-alkyl)*-12*H-benzo[b]phenothiazines* V, Table 1).

A mixture of aryl-amido/imido-alkanols (0.02 mol) and IV (0.02 mol) was dissolved in conc. H_2SO_4 (50 ml) with stirring and cooling for 1 hr. The reaction mixture was further stirred at room temperature for half an hour. Thereafter, it was poured into water and stirred vigorously. The separated solid was filtered, washed repeatedly with water, dried and recrystallised from ethanol to get V (yield 40-50%).

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References

1 (a) Clare N T, Witten L K & Eilmer D S, *Aust Vet J*, **23** (1947) 344.
(b) Clare N T, *Aust Vet J*, **23** (1947) 340.

2 Douglass J R, Baker N F & Longhwest M W, *Am J Vet Res*, **17** (1956) 318.

3 Collier H O J, *Nature*, **146** (1940) 232.

4 Collier H B, *Can J Res*, **188** (1960) 345.

5 Craig J C & Tate H F, *Progr Drug Res*, **3** (1901) 75.

6 Ray D K, Bhopale K K & Srivastava V P, *Ann Trop Med Parasitol*, **72** (1978) 55.

7 Buc S R, *J Am chem Soc*, **69** (1947) 254.

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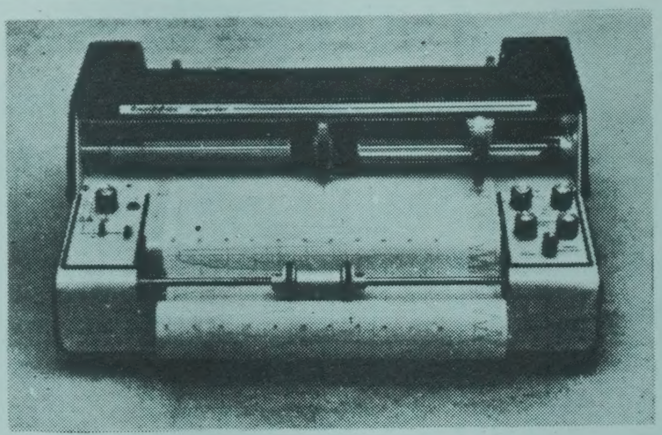

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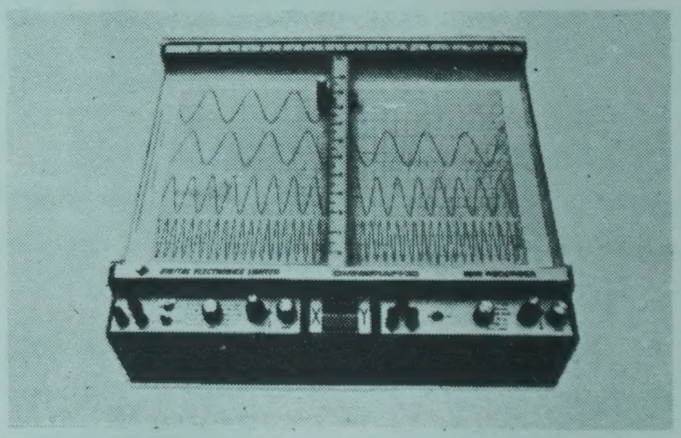

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